Roll Compaction Integrated Work stream

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Thesis submitted for the degree of Doctor of Philosophy

Supervised by

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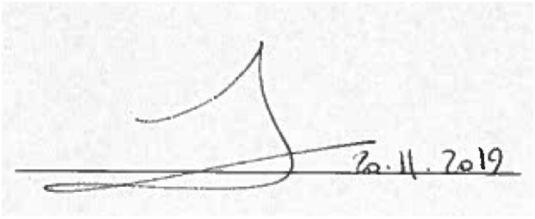
2019

Declaration

The substance of this thesis is the original work of the author, under the supervision of Prof. Gavin Walker and Dr. Maurice Collins. Due reference and acknowledgement has been made, when necessary, to the work of others. No part of this thesis has been previously submitted to this or other university.



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This thesis was defended on 20 September 2019.

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Acknowledgements

Firstly, I would like to thank my supervisors, Prof. Gavin Walker and Dr. Maurice Collins for taking a chance on me and allowing me to pursue a research area, which remained challenging and exciting throughout the PhD. Then, I would like to thank my husband, Saeed for supporting me during my PhD.

I would like to express special thanks to the Solid State Pharmaceutical Centre (SSPC) and Science Foundation Ireland (SFI) for financial support and equipment thought my PhD project.

Finally, I would like to thank my family, especially my parents Khadijeh and Majid for supporting me and my sisters, Maedeh, Marieh and Mehrnaz.

Abstract

This thesis focuses on the study of powder and granule characterization in order to improve the formulations and properties of solid oral dosage forms as final products. The main goal is to investigate the effect of excipients on formulation, granule properties and morphology and on the active pharmaceutical ingredient (API) release rate of final products. Release rate and controlled-release behaviour of drugs are considered as the main quality attributes of products in this project. A natural biopolymer, Alcell lignin is used as an excipient to modify formulations and granule properties in order to improve the final quality of products. In addition, the effect of lignin on drug release and controlled release behaviour is studied.

Firstly, powder and granule properties are investigated using dry granulation by the roll compaction process considering various formulations and process parameters. Then, tablet properties are studied using dry granulation via the roll compaction process, considering lignin as excipient and acetylsalicylic acid as API. The influence of lignin on the drug release rate is assessed using gastric fluid (pH 1.2).

Subsequently, artificial neural network (ANN) is applied for the prediction of drug release. ANN is developed considering the following parameters: roll pressure, screw speed and lignin content. The model was developed and validated through comparison with obtaind experimental data. Compatibility was observed, thereby confirming the model as a predictive model tool for release rate determination.

Finally, the controlled release behaviour of drugs are investigated considering modified lignin as an excipient using varying formulations. Here, paracetamol is considered as an API in all formulations. The results show the positive influence of adding modified lignin as an excipient, as it increases the drug release rate. Moreover, controlled release behaviour of drugs is investigated at different pH, gastric (pH 1.2) and intestine fluid (pH 7.2) and results show pH-sensitive behaviour when modified lignin is utilised in the formulation lignin.

The thesis is presented in “thesis by publication” format. Each chapter corresponds to a published peer review article.

Introduction

Recently, a number of researchers have focused on Alcell lignin for use in pharmaceutical studies because of its low toxicity, biodegradability and biocompatibility properties. Various functional groups in the lignin structure including; phenolic, aliphatic hydroxyl and carboxyl groups offer the possibility for chemical modifications for drug delivery and controlled release. The goal of this project is the use of lignin as natural biopolymer in order to improve formulation and granule properties, as well as, investigative its role in drug release rate and controlled release behaviour.

Chapter 1 introduces a process map, which shows a relation between process parameters, and quality attributes of products using different formulations. Dry granulation by roll compaction is used to produce granules. Alcell lignin is added as an excipient to improve formulations properties. The critical process parameters, which are considered in roll compaction processes are roll pressure and screw speed. The key quality attributes are ribbon density and granule size distribution. The relation between process parameters and quality attributes are mapped using JMP software. Powder characterization is carried out considering different excipients and formulations, then mapped, in order to explain the relation between powder process parameters and ribbon density. Afterwards, the relation between roll pressure and screw speed as process parameters with d50 of granules are mapped. The results illustrate that, roll pressure is the critical process parameter, an increase in roll pressure leads to an increase in the ribbon density and D50 of granules.

Chapter 2 investigates the tablet properties and drug release rate using different excipients and acetylsalicylic acid as API. Dry granulation by roll compaction is carried out to produce granules. The main focus of this study is to determine the influence of lignin as a natural biopolymer on the drug release rate in gastric fluid considering two different formulations. The drug release rate investigation is performed utilizing dissolution and disintegration tests using medium buffer with pH of 1.2. Results show higher release rate, faster disintegration time and higher hardness for the formulation containing lignin. Higher release rate of tablets with lignin formulation are due to the

amorphous structure of lignin and its interaction with the API, which improves drug solubility and therefore bioavailability, the key factor in oral dosage development. On the other hand, higher roll pressure leads to more densified ribbons associated with lignin blends and consequently, larger granules are produced. These larger granules result in porous tablets, which leads to faster disintegration times as solute diffuses faster into the tablets. Also, the higher hardness for tablets containing lignin is attributed to better affinity between lignin and MCC which leads to lignin acting as a tablet binder.

Chapter 3 focuses on modelling of drug dissolution release rate and the effect of lignin using dry granulation by roll compaction process. An artificial neural network (ANN) model considers two hidden layers and combines various activation functions, i.e. linear, hyperbolic tangent, and Gaussian is applied to develop a model in order to design and predict the drug release rates. In order to investigate the effect of lignin as a natural biopolymer on the drug release rate, two different formulations are considered, one with lignin and another without lignin. Lignin is added as an excipient in order to study the bioavailability enhancement of the poorly water-soluble drug. The results of release rate indicated that the tablets containing lignin have higher release rates of API. The results of ANN modelling revealed that the developed model could predict the release rate with high accuracy and R^2=0.99 was obtained for most cases. The model was used to predict the kinetics and equilibrium of the release rate and suitable agreement was obtained between the predicted and measured data. The validated model was then used to understand the effect of process parameters on the release rate, and it was revealed that increasing roll pressure decreases the release rate, because larger granules are produced which in turn results in lower release rate.

Chapter 4 progresses the controlled release behaviour and pH-sensitive properties of drug using modified lignin as an excipient. Three different formulations are considered to study the effect of modified lignin on drug pH-sensitive behaviour and controlled release properties. The first formulation contains microcrystalline cellulose (MCC101) as excipient and paracetamol as active

pharmaceutical ingredient (API). The second formulation includes Alcell lignin and MCC 101 as excipient and paracetamol, and the third formulation consists of carboxylated Alcell lignin, MCC 101 and paracetamol. Due to different functional groups in lignin structure, it is known as a suitable candidate for functionalization. Here lignin modification is carried out by increasing carboxyl groups on the lignin structure. FTIR analysis is performed to show the successful lignin functionalization. Afterwards, in order to investigate the pH-sensitive properties of drug release, dissolution tests are performed on gastric and intestinal fluid, i.e. pH 1.2 and pH 7.2 respectively. The results illustrated the pH- responsive behaviour for formulation containing modified lignin. Drug release rate is studied by dissolution tests for different formulations using buffer solution with pH 5.8, as mentioned in United States pharmacopeia (USP 23). The results showed higher release rate for the formulation containing carboxylated lignin.

Chapter 5 summarizes the key achievements of each chapter and explores ongoing and future work.

Published articles

1) **M. Pishnamazi**, S. Casilagan, C. Clancy, S. Shirazian, J. Iqbal, D. Egan, C. Edlin, D.M. Croker, G.M. Walker, M.N. Collins, Microcrystalline cellulose, lactose and lignin blends: Process mapping of dry granulation via roll compaction, Powder Technology, 341 (38-50), (2018).

2) **M. Pishnamazi**, J. Iqbal, S. Shirazian, G.M. Walker, M.N. Collins, Effect of lignin on the release rate of acetylsalicylic acid tablets, International Journal of Biological Macromolecules, 124 (354-359), (2018).

3) **M. Pishnamazi**, J. Iqbal, S. Shirazian, G.M. Walker, M.N. Collins, Application of Lignin in controlled release: Development of predictive model based on artificial neural network for API release, 26 (6165-6178), (2019).

4) **M. Pishnamazi**, H. Hafizi, S. Shirazian, G.M. Walker, M.N. Collins, Design of controlled release system for paracetamol based on modified lignin, 11 (1059), (2019).

5) Keshavarz L., Steendam R. R. E., Blijlevens M. A. R., **Pishnamazi M**. & Frawley P. J. Influence of Impurities on the Solubility, Nucleation, Crystallization and Compressibility of Paracetamol, Cryst. Growth Des,19 (4193-4201), (2019).

Presentations

1) Optimization of microcrystalline cellulose and lignin for dry granulation of pharmaceutical formulations, ECO-BIO 2018 conference, Dublin, **Oral presentation**.
2) Development of a process map for dry granulation by roll compaction, 8th International Granulation Conference, 2017, Sheffield, **Oral presentation**.
3) Roll compaction integrated work stream in pharmaceutical manufacturing: population balance modeling, 10th World Congress of Chemical Engineering, 2017, Barcelona, **Oral presentation**.

4) Continuous dry granulation of pharmaceutical powder using roll compaction process, EUPAT8 conference, 2016, Cork, **Poster presentation**.
5) Design of controlled release system for paracetamol based on modified lignin, Bioengineering conference 2019, Limerick, **Oral presentation.**
6) The influence of lignin on API content uniformity in continuous Twin-Screw wet- granulation process, 9th International granulation conference 2019, Lausanne, **Poster presentation**.
7) Influence of Impurities on the Solubility, Nucleation, Crystallization and Compressibility of Paracetamol, 2019 AIChE Annual Meeting.

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Chapter 1.

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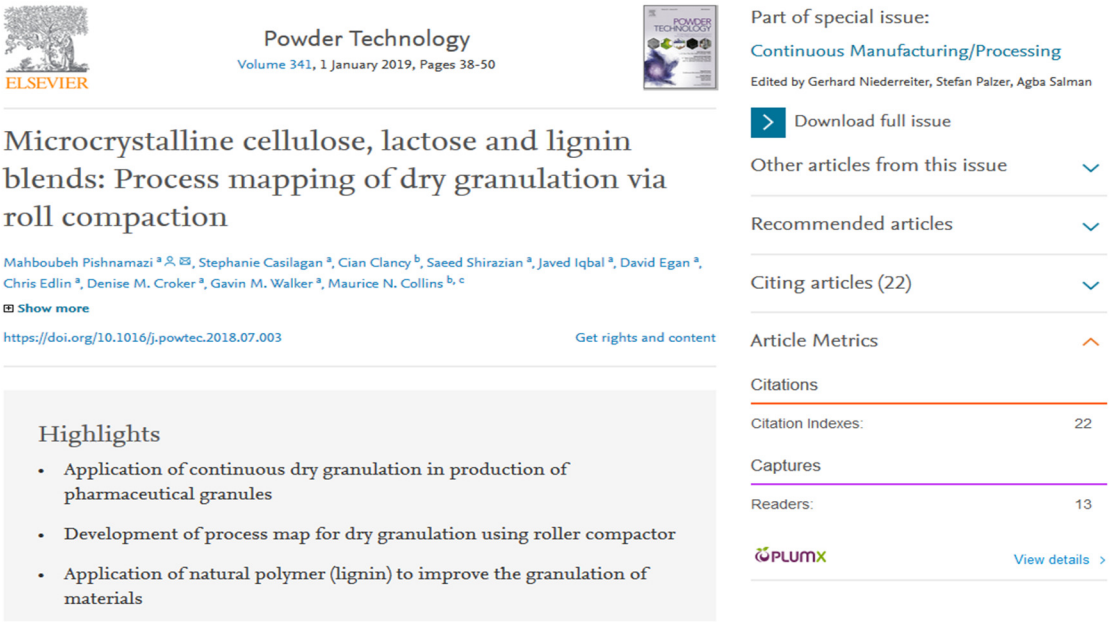

ELSEVIER

Powder Technology
Volume 341, 1 January 2019, Pages 38-50

Microcrystalline cellulose, lactose and lignin blends: Process mapping of dry granulation via roll compaction

Mahboubeh Pishnamazi [a], Stephanie Casilagan [a], Cian Clancy [b], Saeed Shirazian [a], Javed Iqbal [a], David Egan [a], Chris Edlin [a], Denise M. Croker [a], Gavin M. Walker [a], Maurice N. Collins [b, c]

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Highlights

- Application of continuous dry granulation in production of pharmaceutical granules
- Development of process map for dry granulation using roller compactor
- Application of natural polymer (lignin) to improve the granulation of materials

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Microcrystalline Cellulose, Lactose and Lignin Blends: Process Mapping of Dry Granulation via Roll Compaction

Mahboubeh Pishnamazi[1,*], Stephanie Casilagan[2], Cian Clancy[3], Saeed Shirazian[1], Javed Iqbal[2], David Egan[2], Chris Edlin[2], Denise M. Croker[1], Gavin M. Walker[1], Maurice N. Collins[3]

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Abstract

In this study, a process map was developed in an effort to improve the understanding of dry granulation of pharmaceutical excipients by roll compaction process, and to implement the quality-by-design (QbD) approach. Through development of the process map, a correlation was made between the critical process parameters (roll pressure, screw speed), and critical quality attributes (density of ribbons and granule size). This method reduces development time, quantity of materials required and cost. A new excipient formulation based on natural polymers (lignin and cellulose) was utilised to improve the properties and reduce costs associated with tablets production. A variety of lignin, microcrystalline cellulose (MCC) and lactose monohydrate formulations were compacted followed by milling to obtain granules. Formulations were also characterised in terms of compressibility and flowability. Density of ribbons as well as granule size distribution were mapped versus critical process parameters. Based on this work as initial study, roll pressure was found to be a critical process parameter, higher ribbon density and larger granule size obtained with higher roll pressure. It was also revealed that the process map is a powerful tool in understanding the dry granulation, and can be used to construct a design space for pharmaceutical manufacturing.

Keywords: Dry Granulation; Roll Compaction; Critical Process Parameters; Critical Quality Attributes; Quality by Design; Process Map; Natural Excipient; NIR Spectroscopy

1. Introduction

The current practice in pharmaceutical manufacture is batch wise in which trial and error approach, which is time-consuming and wasteful is used for new formulations and equipment. Recently, continuous processing has received more attention in the pharmaceutical industry as it offers superior characteristics compared to batch processing [1]. Upon developing continuous processing, we can avoid scale-up issues, reduce cycle times, variability and production costs, ensure faster product release, increase flexibility and efficiency, and improve product quality [2, 3]. Underpinning research is required to transform batch mode operation to the continuous mode. One of the key processing steps in the pharmaceutical manufacturing is granulation, as the properties of final products are dependent on the granule properties. In the manufacturing process, active pharmaceutical ingredients (API) and excipients mixtures are granulated to improve flowability and content uniformity of the particles. There are two main methods for granulation of pharmaceutical formulations, namely dry and wet granulation [4, 5]. In wet granulation, liquid binders are used to form granules from fine powder, whereas in dry mode no binder is required. Indeed, dry granulation is useful for compounds that are sensitive to heat and moisture [6-8]. Roll compaction (RC) is widely used for dry granulation as a continuous process, and has shown more advantages, for example, a reduction in powder segregation and increasing bulk density [7, 9-11].

During roll compaction, fine powder is compacted between two counter-rotating rolls to produce ribbons (briquette) by applying hydraulic force on powder. The ribbons are milled to produce granules, and then compacted to form tablets [11, 12]. As such, controlling ribbon density and granule size are critical in RC process. Therefore, application of RC would promote the paradigm of continuous pharmaceutical manufacturing. In order to develop a continuous line for manufacturing of solid-dosage forms, the process understanding is of great importance so that the critical quality attributes of products are correlated with the process parameters and material properties [13-16].

The mechanism of the dry granulation process is still not well understood in the continuous pharmaceutical manufacturing context. Several models have been deployed such as Johanson model, slab method, finite element method, discrete element method and artificial neural network to correlate the process parameters with ribbon density. These models are of mathematical basis and are used to predict process variations [8, 11-13, 16, 17]. In addition, several researchers have studied different aspects of RC to understand the effect of process parameters on ribbon density [18-23].

McAuliffe et al. [24] studied the effect of roll pressure on density of ribbons prepared with a formulation containing MCC 102, anhydrous lactose, and they highlighted the impact of roll pressure on ribbon and granule properties at constant screw and roll speed with variable roll gap. They mentioned increasing the roll pressure causes decrease in the roll gap. In addition, it was shown that increasing the roll pressure, have a significant effect on ribbon and granule properties. Souihi et al. [25] investigated the influence of process parameters on ribbon density using the Johanson model for the formulation containing paracetamol, mannitol, and MCC 102. They mentioned that Johanson model describes the effect of roll pressure and screw speed on ribbon density and emphasised the minor effect of roll gap on ribbon density compared to roll pressure. Khorasani et al. [21] also studied the effect of roll pressure and roll speed on ribbon density utilising a formulation containing MCC 101 and acetylsalicylic acid with the constant roll gap. Moreover, the screw speed was adjusted automatically to keep the roll gap constant. It was also shown that increasing the roll pressure leads to increase the ribbon density and granule size. On the other hand decreasing the roll speed results in increasing ribbon density and granule size due to increased residence time of powder between rolls. Kumar et al. [26] studied the influence of process parameters on quality attributes of the wet granulation process by developing a regime map for a formulation consisting of α-Lactose monohydrate and PVP. It was shown that the regime map provides a design space for optimisation of granulation. Sajjia et al. [2] analysed the effect of process parameters on ribbon density using of MCC 102, and further explained the effect of roll pressure and screw speed on ribbon density. They believed

that increasing the roll pressure leads to ribbons with higher density. They further highlighted the unstable and minor effect of screw speed on ribbon density.

As mentioned, different researchers have studied the effect of process parameters on ribbon density and particle size of granules, but development of a comprehensive process map, which is capable of providing a design space for roll compaction process, is of great importance. Furthermore, the effect of formulation on the ribbon and granule properties has not been studied. None of these investigations have shown the correlation between process parameters and quality attributes by mapping the process, and understanding the influence of material formulation.

Indeed, a comprehensive understanding the process for various formulations is of great importance. In order to determine the best design space in dry granulation processing, one may need to use a wide range of DoE (design of experiments) to fully understand the effect of underlying parameters on ribbon properties as well as granule size. Development of a design space for dry granulation can be achieved with a process mapping, which correlates the process input to the outputs for a wide range of formulations. Recently, several researchers have attempted to show the importance of identifying the interaction between process parameters of materials and quality attributes of products for roll compaction process. They have utilised dimensionless variables for roll compaction, and regime maps for wet granulation, then processing have been investigated [15, 23, 26-28]. The process map has been successfully developed for wet granulation via twin-screw extruder [26], and it was shown that the process map concept is of great importance for the development of continuous manufacturing. Therefore, it would be of great importance to develop a process map for dry granulation by roller compactor considering new formulations.

Lately, due to different issues in terms of side effects and drug release, use of natural polymers has attracted much attention on the development of tablet formulations through usage of new excipients. Natural polymers offer a number of advantages as excipients in tablet manufacture including; low or no toxicity, regulatory compliance and stability, while enhancing the physicochemical properties of

powders and increasing drug release rates. Due to the high chemical functionality of lignin, it can be introduced as a novel excipient for development of new materials [29-37].

In the present study, a process map has been developed for RC processing with various formulations including the novel lignin excipient. Different formulations with differing percentages of microcrystalline cellulose (MCC), lactose and Alcell lignin were designed and used throughout the experiments. For designing the process map, a correlation between input variables including roll pressure, screw speed, and ribbon properties such as density as well as D50 of granules was found. This method reduces development time, quantity of materials and cost. It should be noted that these process maps are a preliminary study and are limited to the specific type of formulations and equipment used in the experimental design. Moreover, in order to assess the applicability of NIR spectroscopy as a PAT tool for on-line monitoring of RC, the density of ribbons containing bio-based materials were analysed using the NIR method. However, it was conducted as an off-line experiment and for limited samples.

2. Experimental procedure

2.1. Materials and methods

Microcrystalline cellulose (MCC SANAQ® 102 L USP/NF/EP), lactose monohydrate (Lennox USP, NF, BP, Ph, pure pharma grade) and Alcell lignin (Tecnaro, Ilsfeld, Germany) were used as excipients throughout the experiments. In order to prepare the excipient mixtures, microcrystalline cellulose, lactose monohydrate and Alcell organosolv lignin were mixed with 0.5 % w/w magnesium stearate (Sigma-Aldrich), which acted as lubricant. For further details on the lignin used in this study the authors are referred to [38]. Two different formulations were considered, first, MCC was mixed with 5, 10 and 20 wt. % of lactose, and then MCC was mixed with 5, 10 and 20 wt. % of Alcell lignin. All components were blended using a Morphy Richards Stand Mixer with beater attachment at speed setting 3 (100 RPM approx.) for 15 min.

2.2. Equipment and analysis

A top-fed roller compactor Freund TF-MINI (Vector Corporation, Japan) (see Figure 1) with a vertical screw feeder was utilised throughout the RC experiments. The width and diameter of rolls

were 25 and 100 mm, respectively. The roll speed was set at 4 rpm for all experiments. Process parameters, screw speed (SS) and roll pressure (RP), were changed with variable screw speed (8-18 rpm) by 2 rpm step and roll pressure (10-50 bar) by 5 bar step. An envelope density analyser, (GeoPyc 1360, Micromeritics Instrument Corp. 4356 communications Drive, Norcross, GA 30093, USA) was used to measure the ribbon density. The roll gap was uncontrolled and variable during the experiments. The thickness of produced ribbons was measured to be between 1 – 3 mm for all samples.

In addition, a multipoint Near-Infrared (NIR) spectrometer (Innopharma, Ireland), Multieye NIR, was utilised to characterise the ribbon density. The NIR spectra were calibrated using the density obtained via the GeoPyc instrument and developing a calibration model. Partial Least Square (PLS) technique was used for calibration of NIR results. The produced ribbons were milled with a conical mill (Laboratory Comil 193 AS, Quadro, USA) with 813-µm mesh size at 3000-rpm mill speed to produce granules.

The particle size distribution (PSD) of powders and post-milling granules were measured using Microtrac S3500 particle size analyser (Malvern, USA). Powder flow and compressive behaviour of materials were evaluated using powder flow rheometer (FR4, Freeman Technologies, UK). For characterising the morphology of powders, scanning electron microscopy (SEM) was performed under vacuum. Particle shape and surface morphology of the powders were examined using a scanning electron microscope (Hitachi TM-1000 desktop SEM, USA). Schematic representation of the roller compactor and the photo of sieve mill and RC are shown in Figure 1.

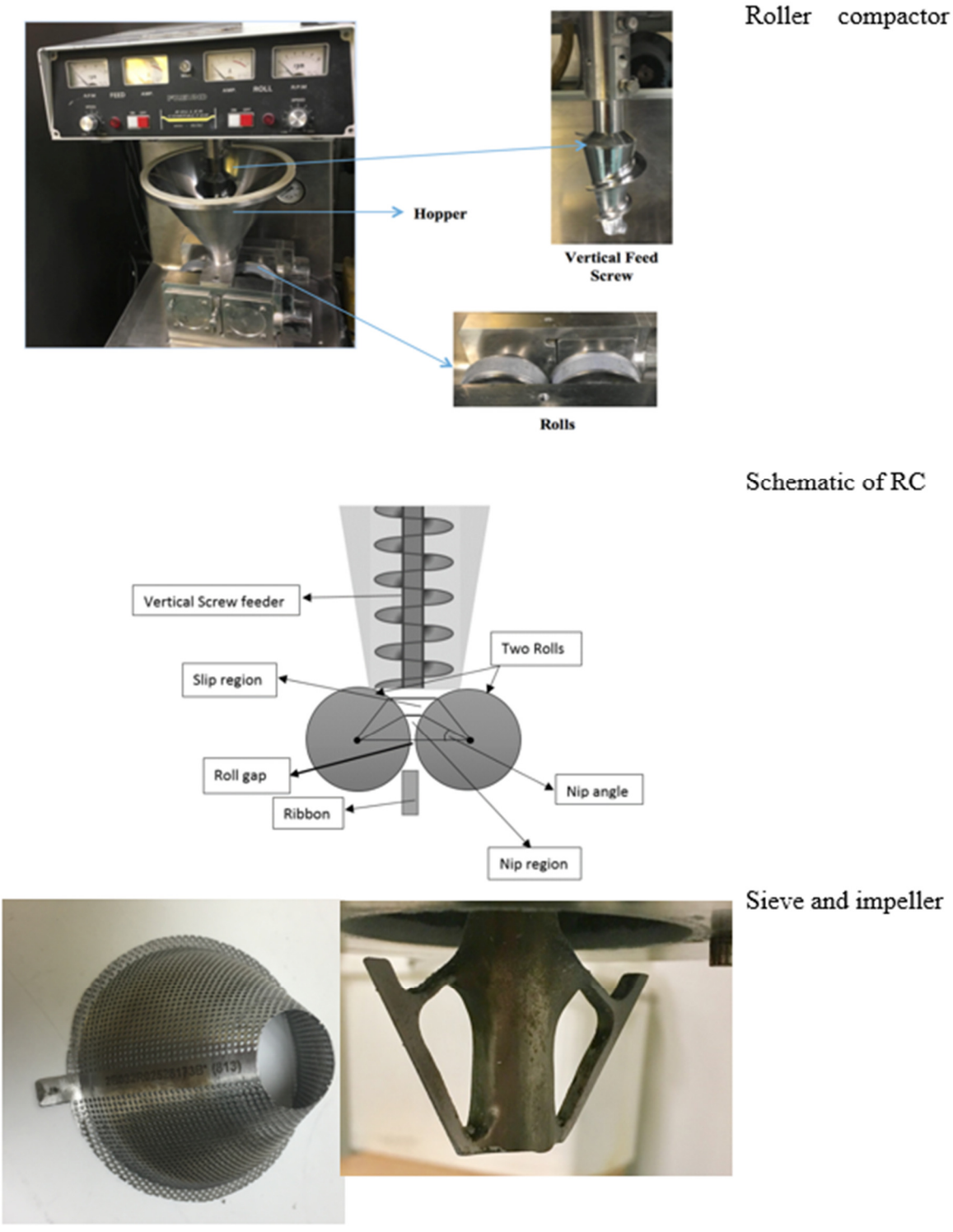


Figure 1. Freund roller compactor, mill, impeller and sieve used in experiments.

3. Results and discussions

3.1. Effect of process parameters on ribbon density

In order to implement the quality by design (QbD) approach for roll compaction process, first, a relationship between process parameters and quality attributes of products should be defined. For developing a basic understanding of dry granulation process by roller compactor, the effect roll pressure and screw speed on ribbon envelope density are plotted by using *JMP 12 pro* software and shown in Figure 2. As expected, the ribbon envelope density is greatly influenced by roll pressure, while screw speed has minor effect on the density.

It should be pointed out that in some cases, insufficient data were collected due to process limitations at these operating conditions. It is observed that applying more roll pressure, at constant screw speed, leads to denser powders, and consequently produced ribbons with higher density for all samples. Higher roll pressure under constant screw speed leads to more compaction between two rotating rolls and thereby higher density of ribbons. In other words, in constant screw speed, the amount of powders and powder residence time between the rolls are constant as well, and more pressure results in more roll force and more densification of ribbons. The graphs of different percentages of lactose illustrate wide range of process parameters, while the graphs with lignin show more limitations in terms of screw speed.

Furthermore, it is observed that at the same content of lactose and lignin in the formulation, higher ribbon density is obtained for the formulation containing lignin, which could be attributed to the intrinsic physical and chemical properties of lignin, such as amorphous and cross-linked structure and interaction with MCC, which will be further investigated in the next section. On the other hand, as it can be seen in Figure 2, screw speed has a minor influence on the ribbon density for all formulations. For each formulation with the same roll pressure, increasing the screw speed results in increased ribbon density, although slightly. As shown in Figure 2, more limitations of process parameters are observed for higher percentages of lactose formulation. The results confirm that lignin is a promising bio-based excipient for tablet manufacturing and almost similar behaviour with

common excipients (e.g. lactose) was observed for the formulations containing lignin.

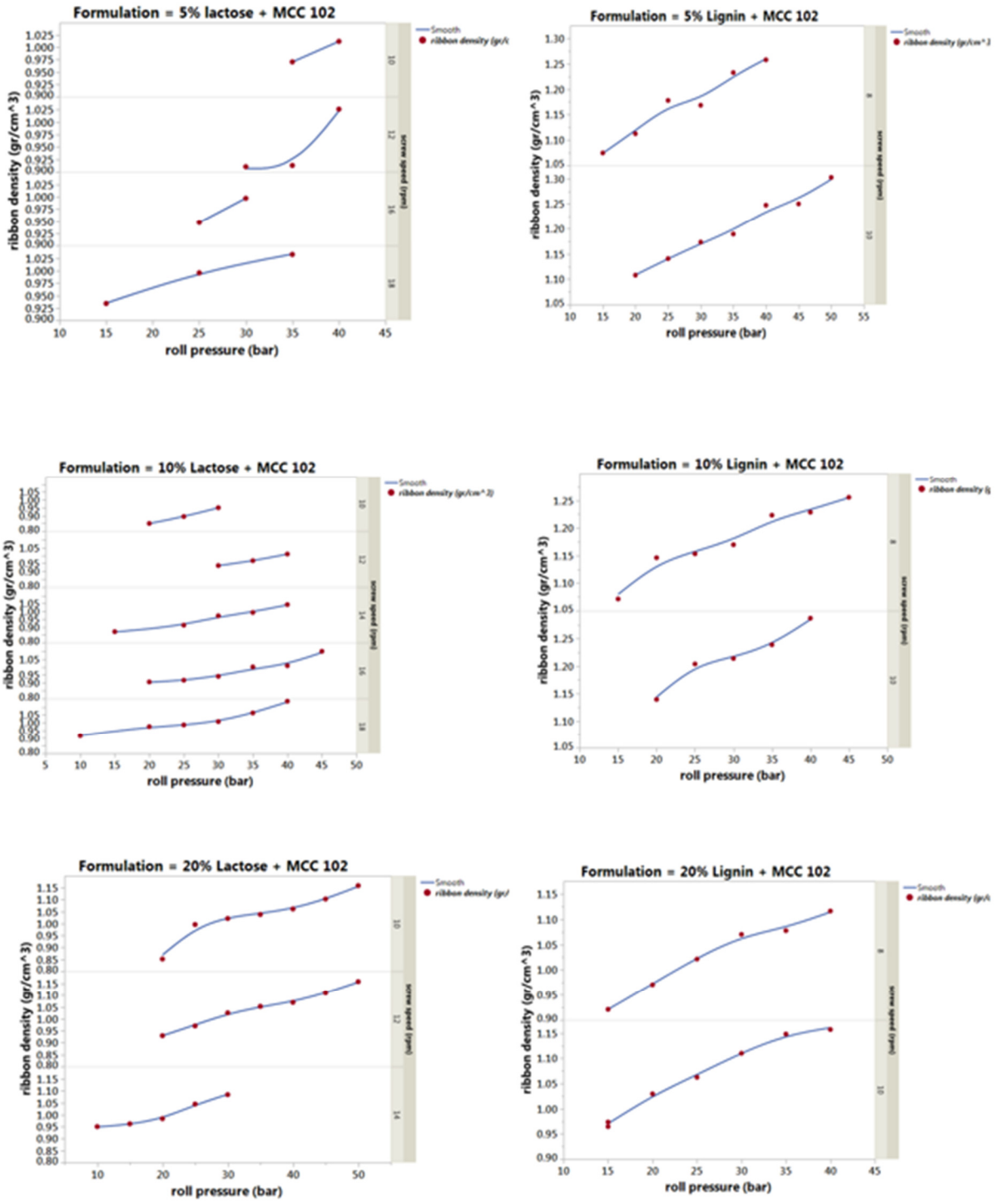


Figure 2. Effect of process parameters on ribbon density for various formulations.

3.2. Effect of formulation on density of ribbons

To investigate the effect of the formulations used on the density of the produced ribbons, contours of density versus roll pressure and screw speed for different formulations are plotted as shown in Figures 3 and 4. These contours show the two-dimensional colour representation for the relationship between process parameters specified and the ribbon density.

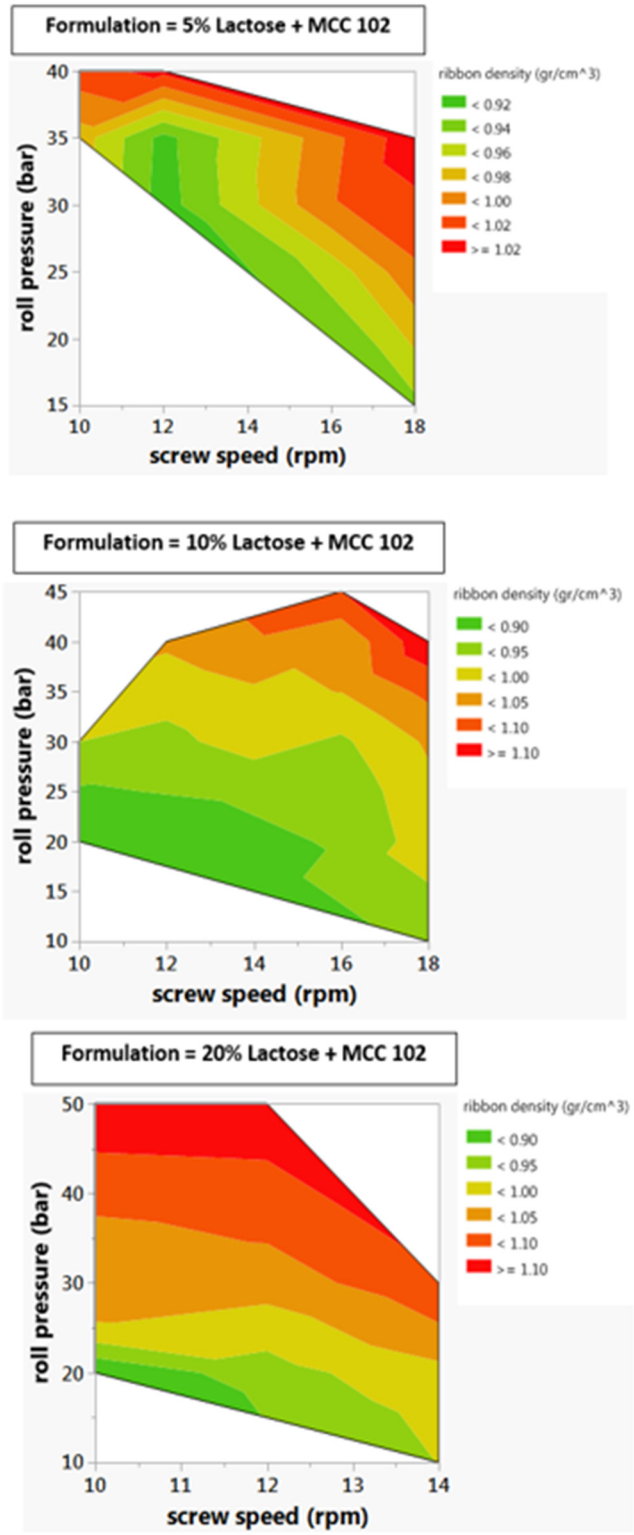


Figure 3. Contours Plot for Density (g/cc), Formulation = 5, 10 and 20 % Lactose.

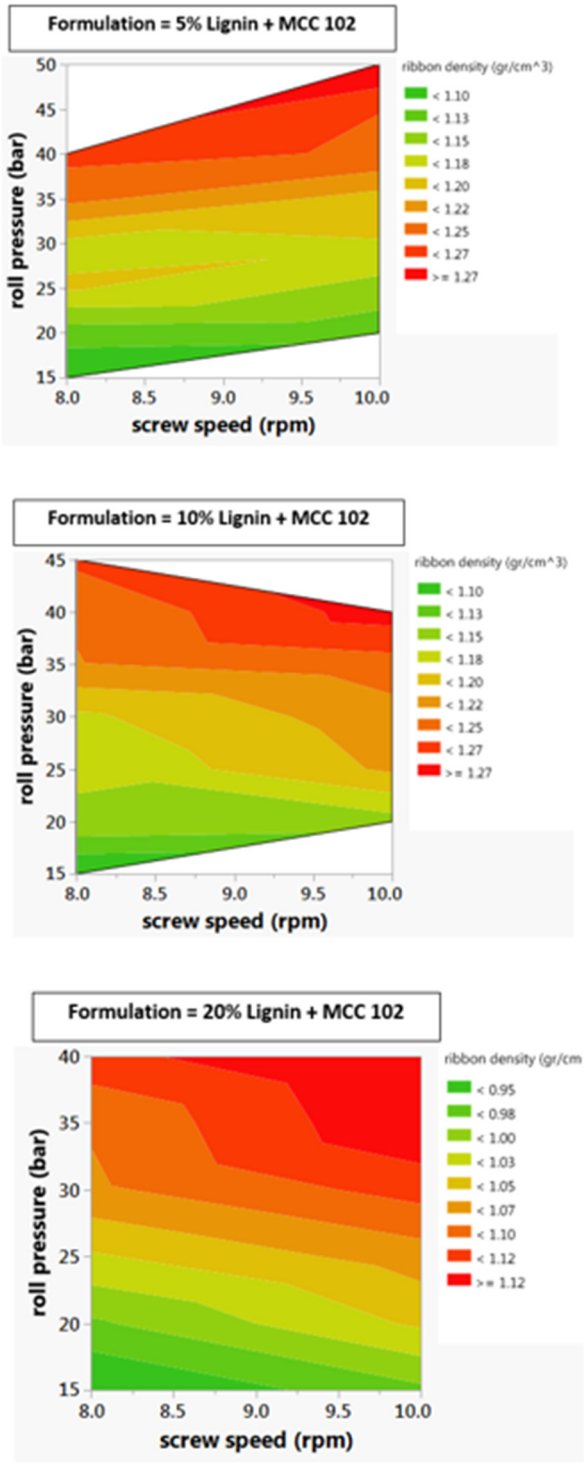


Figure 4. Contours Plot for Density (g/cc), Formulation= 5, 10 and 20 % Alcell lignin.

Figure 3 shows the contours of formulation with lactose at different percentages in which the white area, at the background of the map, indicates the process limitations. The latter means that the experiments cannot be conducted due to operational problems such as roller blockage, over compaction, etc. In terms of blockage of materials, it happened at the end of screw feeder, the neck

of hopper, in the slip region (see Fig. 1). As such, these contours also indicate the workability of RC in which the colour areas correspond to the working conditions of equipment.

It is observed that increasing the percentage of lactose results in higher density and less limitation in the process parameters. Furthermore, by increasing the percentage of lactose, the effects of screw speed on ribbon density decay. At 5% of lactose, increasing the screw speed leads to enhancing the density of ribbon slightly, whereas for 10% of lactose, the screw speed influence is slight, and for 20% of lactose it does not have any appreciable effect (see Figure 3) which is in agreement with literature [8, 24].

Figure 4 illustrates the contours of formulations with different percentages of Alcell lignin including 5, 10 and 20 wt. percentage. The plots show less limitation in terms of roll pressure specifically with higher percentage of Alcell lignin. Therefore, addition of lignin would improve the process in terms of limitation and a vast range of process parameters can be used for the formulations containing lignin. In terms of the effect of process parameters on ribbon density, higher roll pressure results in higher ribbon density for all percentages of Alcell lignin. Nevertheless, the effect of screw speed on ribbon density is almost negligible. Increasing the screw speed while keeping the roll pressure constant, does not have considerable effect on ribbon density for formulations containing lignin. Given that the roll gap was variable in the experiments, increasing the screw speed increases the amount of powder pushed between the rolls, therefore, the gap between the rollers increases which corresponds to the increase of the ribbon thickness. Now, increasing the ribbon thickness decreases the stress applied on the powder as the force will be distributed over wider thickness of powder. However, this phenomenon is not envisaged to be significant compared to the effect of roll force.

In order to understand the behaviour of various formulations during the roller compaction process, the Stability Index (SI) of different blends were measured by FT4 powder rheometer. The stability index of 1 is ideal and implying that the material does not change during the characterisation. An appropriate explanation is provided in the Appendix about the stability index. The SI of the blends, containing 5%, 10% and 20% lignin were 0.729, 0.752, and 0.840 respectively. It implies that by

increasing the lignin content in the blends, the stability of the powder blends increases. Moreover, the contours graphs show the higher stability for the blends with higher lignin percentage. On the other hands, the stability index was measured for the lactose blends as well. The SI of 5%, 10% and 20% lactose were 0.891, 0.714 and 0.587 respectively. These results illustrate that increasing the lactose percentage, leads to decrease in the blend stability.

For better understanding, the effect of formulations and materials on quality attributes of roll compaction process, flowability and cohesion for different materials used in this work were measured by FT4 powder rheometer and represented in Figure 5.

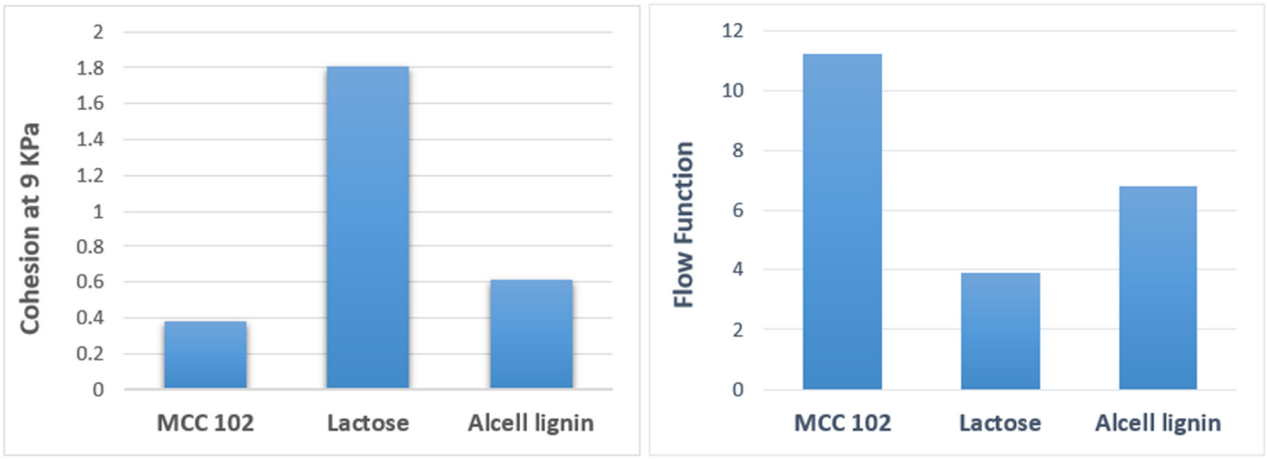


Figure 5. Cohesion and flow function graphs for Lactose, Alcell lignin and MCC 102 measured by FT4 powder rheometer

It is observed that Alcell lignin has a better flowability (Flow Function=6.38, easy flow) than lactose (FF=3.54, poor flow). The methods and equations used for measuring powder flowability are described in Appendix A. On the other hand, lactose has greater cohesion (1.27 kPa) than Alcell lignin (0.611 kPa) and MCC (0.384). To analyse the effect of particle size and shape on the properties of materials, PSD and SEM characterisations were carried out. Figure 6 presents the particle size distribution and SEM of the three used excipients. Image A and PSD of lactose show a wide range of particle size, which results in poor flow behaviour. Image C and PSD of Alcell lignin illustrates a wide range of particle size, similar to lactose, but with lower cohesion which causes easy flow. On the other side, image B and PSD of MCC 102 demonstrates a narrow particle size distribution, which

leads to free flow behaviour. As it is demonstrated in the particle size graph, lactose and lignin have almost similar particle size (D50=37 microns), but MCC 102 has larger particles with a narrower range of particle sizes with more uniformity and higher flowability. In addition, Figure 7 indicates the results of compressibility of the excipients measured by FT4 powder rheometer via compressibility test. Compressibility is a useful indicator of powder flowability, if it is cohesive or free flowing [39, 40].

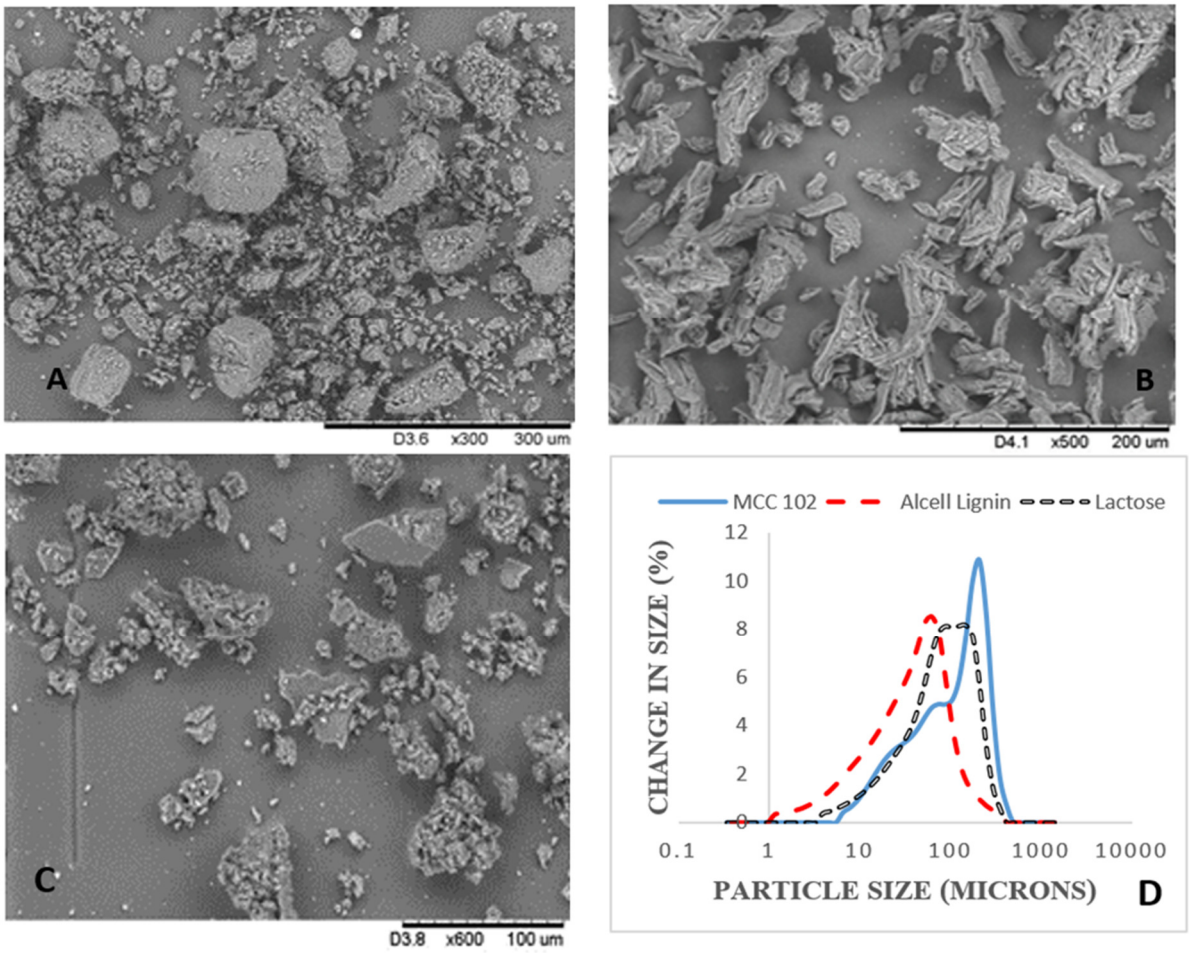


Figure 6. SEM of Lactose (A), MCC 102 (B) and Alcell lignin (C), and particle size distributions (D).

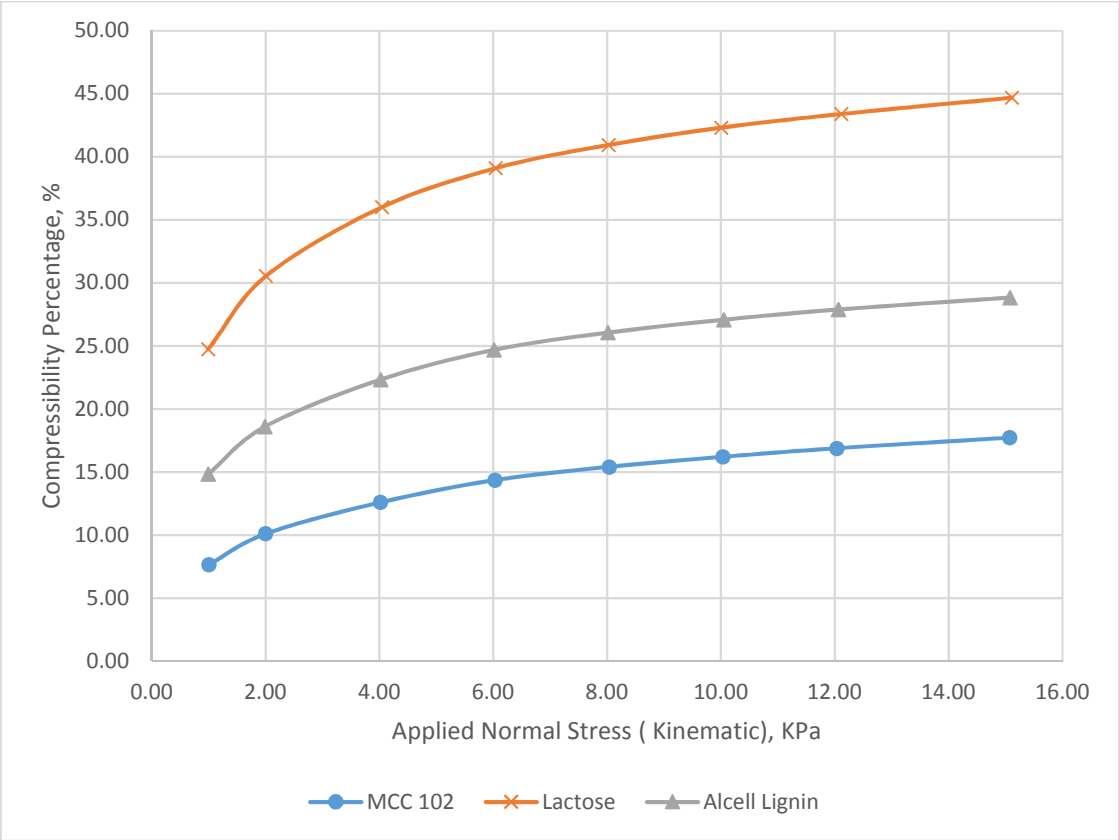


Figure 7. Compressibility of Lactose, MCC 102 and Alcell lignin measured by FT4 powder rheometer.

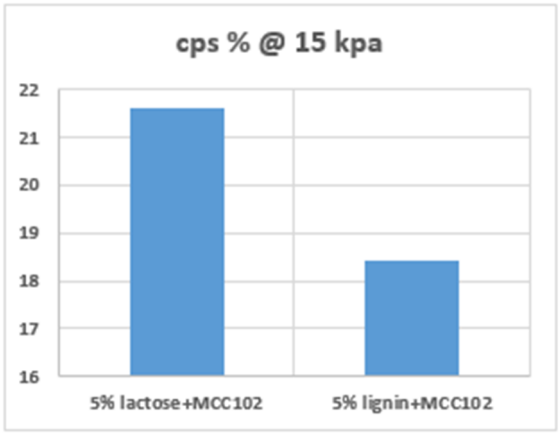
As seen in Figure 7, lactose shows the highest compressibility among all excipients, while MCC 102 has the lowest compressibility. The reason to use lactose/lignin as excipient is to improve the compaction behaviour of MCC 102 in the manufacturing process. Also, it is seen that lignin can be used to improve the compressibility of MCC 102 during the RC process.

The process map indicates that higher compressibility leads to a wide range of process parameters for different formulations containing lactose. However, lactose is cohesive material and poor flowing, and introducing lignin can improve the flow behaviour of formulation. A wide range of screw speeds for the blends with different percentages of lactose are shown in Figure 3 [29-31]. For the lignin, low range of screw speed can be applied during the process (see Figure 4). It means that at higher screw speed, more powders are pushed between the rolls and increasing screw speed would result in blockage due to less compressibility of lignin compared to lactose. On the other hand, higher screw speed works better with more compressible materials like lactose. Comparing the cohesion of lignin

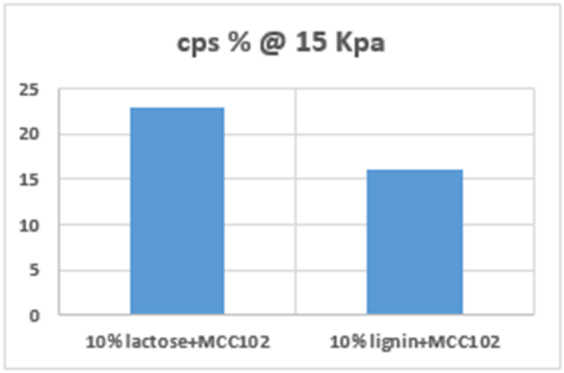
and MCC, lignin has higher cohesion, and increasing the percentage of lignin would result in less process limitations. The higher ribbon density for formulations containing lignin as observed in Figure 4, can be attributed to the affinity and interaction between lignin and MCC 102 as both materials are of cellulosic nature.

Physical properties of powders have an important influence on the quality attributes of products. We have to investigate the physical properties of materials and the behaviour of them as a component in the formulations. There is a relationship between particle size of powders as an inherent properties and their surface area. Materials with smaller particles have larger surface area, which cause them to be more compressible than the material with larger size. Therefore, lactose with smaller particle size indicates increased particle-particle contact which tends to be more compressible compared to MCC 102. For lactose, by increasing applied stress the compressibility increases due to smaller size which results in more efficient inter-particle packing.

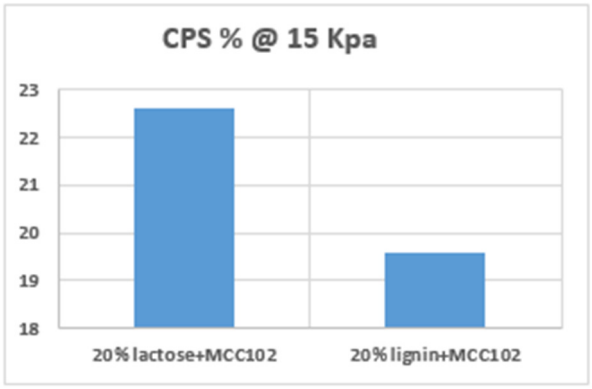
To further understand the effect of blends properties on quality attributes of products, the results of different blends characterisation by FT4 powder rheometer are demonstrated in Figure 8. The results confirm that blends with differing lactose percentages have higher compressibility than the blends with differing Alcell lignin percentages. For example, as shown in the Figure 8A, due to the highest percentage of cohesion of lactose, the blends with lactose are more compressible.



(A)



(B)



(C)

Figure 8. Graphs of compressibility (CPS) of different blends measured by FT4 powder rheometer.

3.3. Effect of process parameters on D50 of granules

Another critical quality attribute for dry granulation using roll compaction is granule size, as the tablet properties are dependent on the granule size. The produced ribbons were then milled to obtain the desired granules. For this section, D50 of granules (median size) was used as representative granule size. The effect of process parameters on D50 of granules for different formulations are illustrated in

Figures 9 and 10. These maps are plotted by using *JMP* 12 pro software (SAS institute) for D50 of granules versus roll pressure and screw speed. Figure 9 illustrates the correlation between process parameters and D50 of granules for 5, 10 and 20 percentages of lactose. For each formulation, higher roll pressure leads to greater D50 at constant screw speed. As discussed, because of smaller particle size of lactose compared to MCC 102, the blends containing lactose are more compactible. Increasing the lactose percentage leads to denser ribbons, and consequently results in larger granules because more shear force is needed to break up the ribbons in the mill for granule formation. In addition, it is seen that the effect of screw speed on D50 at constant roll pressure is almost negligible. Moreover, in the highest percentage of lactose (20 %), due to inherent properties of lactose such as cohesion, a narrow range of screw speed and a wide range of roll pressure are observed. Due to higher cohesion of lactose than MCC 102, in the higher percentage of lactose, there are more limitations. In Figure 10, the correlation between process parameters and D50 of granules for 5, 10 and 20 percentages of Alcell lignin are shown. These maps present a narrow range of screw speed and a wide range of roll pressure for these formulations. Because of Alcell lignin properties including less compressible and less cohesion, smaller D50 of granules were observed for formulations containing lignin. On the other hand, for different formulations of Alcell lignin, increasing the percentage of lignin leads to larger D50 of granules because of smaller particle size of lignin than MCC 102, higher compressibility and higher cohesion of lignin.

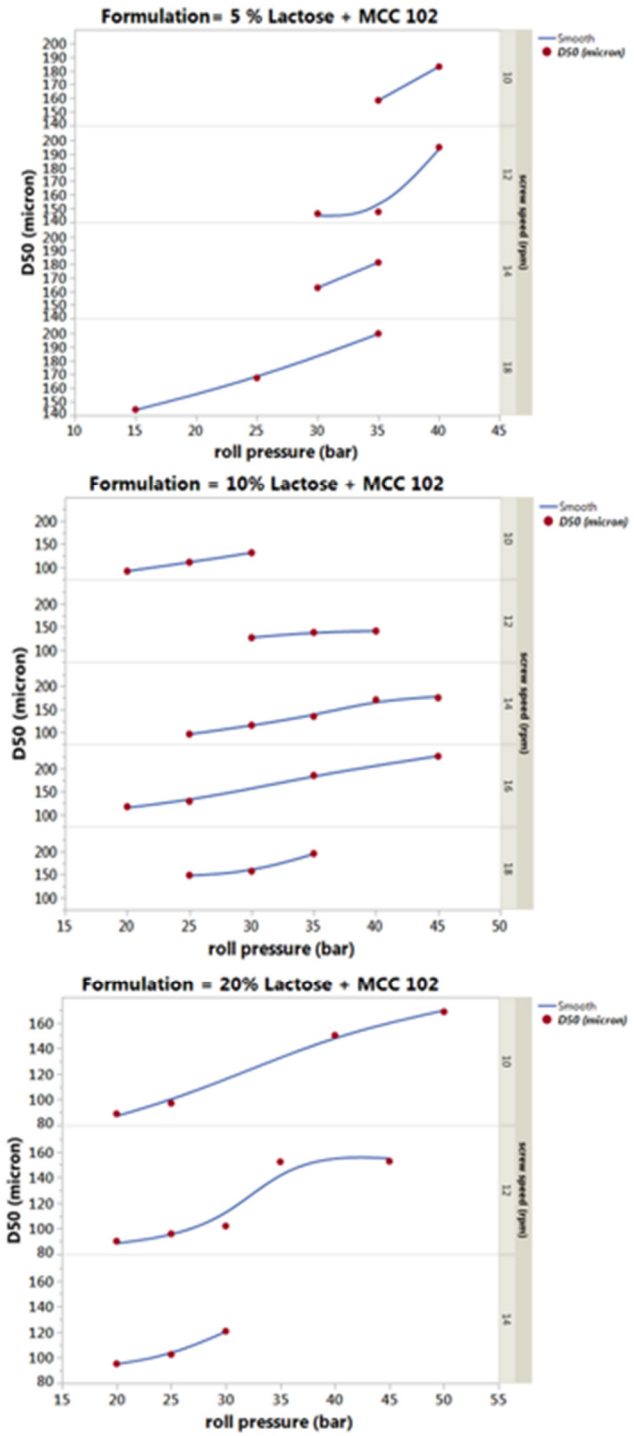


Figure 9. Effect of process parameters on D50 of granules for lactose formulations.

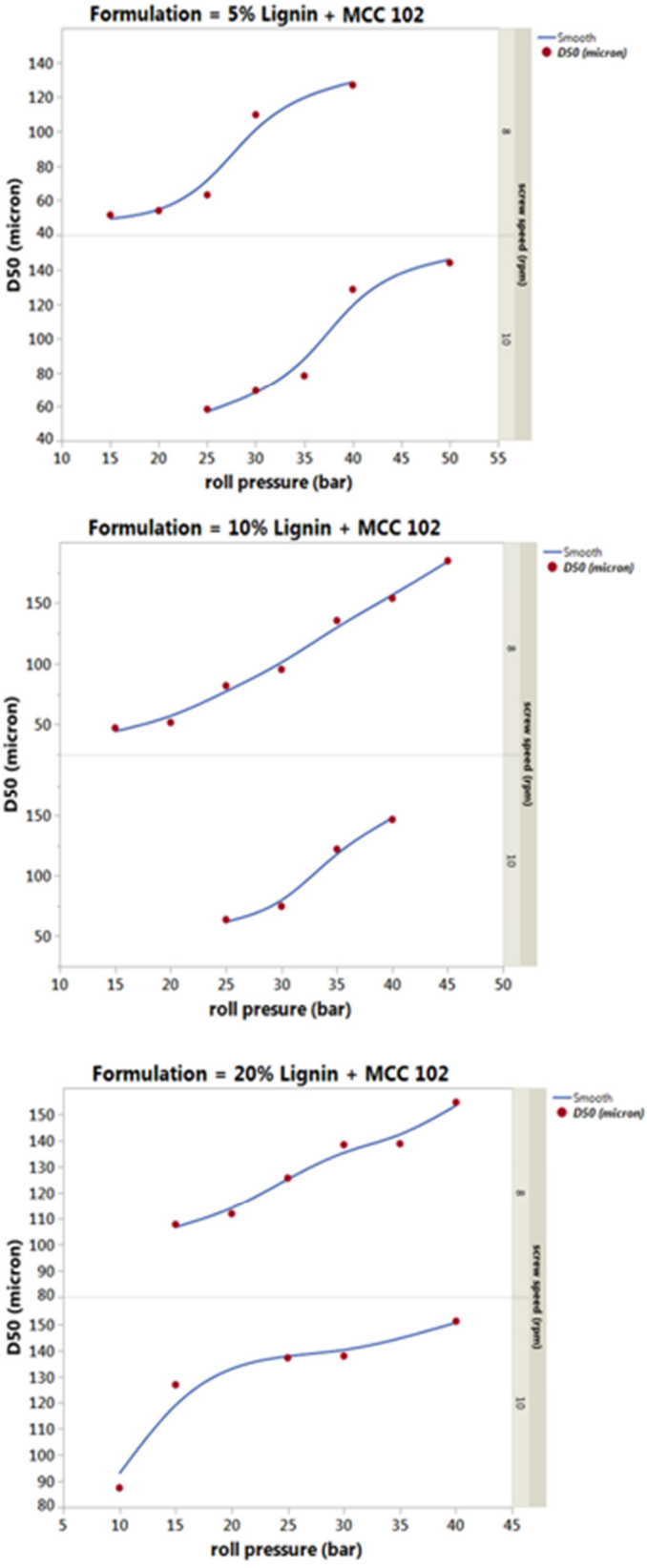


Figure 10. Effect of process parameters on D50 of granules for Alcell lignin formulations.

3.4. Effect of formulation on D50 of granules

The contours of D50 of granules versus roll pressure and screw speed are designed for different formulations of lactose and Alcell lignin, as shown in Figures 11 and 12. These maps describe the limitations of process parameters and equipment as discussed before. The generation of uncontrolled fines is a common problem in dry granulation process. During milling process to produce granules, the particles, which are ≤125 μm, are known as fines [41]. In addition, the area in the process map with particle size smaller than 125 micron for each formulation reveals the amount of fines produced which should typically be avoided.

Figure 12 indicates the correlation between process parameters and D50 of granules for different percentages of Alcell lignin. The same trend was observed for formulation with Alcell lignin. Higher percentages of Alcell lignin leads to larger particle size of granules and less percentage of fines. As discussed before, the compressibility of different blends with lactose are higher than Alcell lignin. It is concluded that, higher compressibility of lactose formulations leads to produce denser and stronger ribbons, then, larger granule size. Less percentage of fines and bigger granule size are observed with 20 wt. % of Alcell lignin compared to lower lignin content. Also, as seen, higher roll pressure leads to greater D50, while as mentioned before, screw speed does not have any serious effect on D50.

These plots, Figures 11 and 12, also show that the amount of fines (particles ≤ 125 micron) are dependent on the roll pressure, increasing the roll pressure leads to denser powders, and larger granule size, result in a reduction in the amount of fines. At a constant roll pressure, increasing the screw speed results in enhancement of the particle size of granules for 5 and 10 wt. % of lactose formulation. However, for 20% of lactose, the screw speed does not have any important influence on particle size of granules, in addition, the map shows more stability. By increasing the roll pressure, the influence on particle size of granules is more prominent.

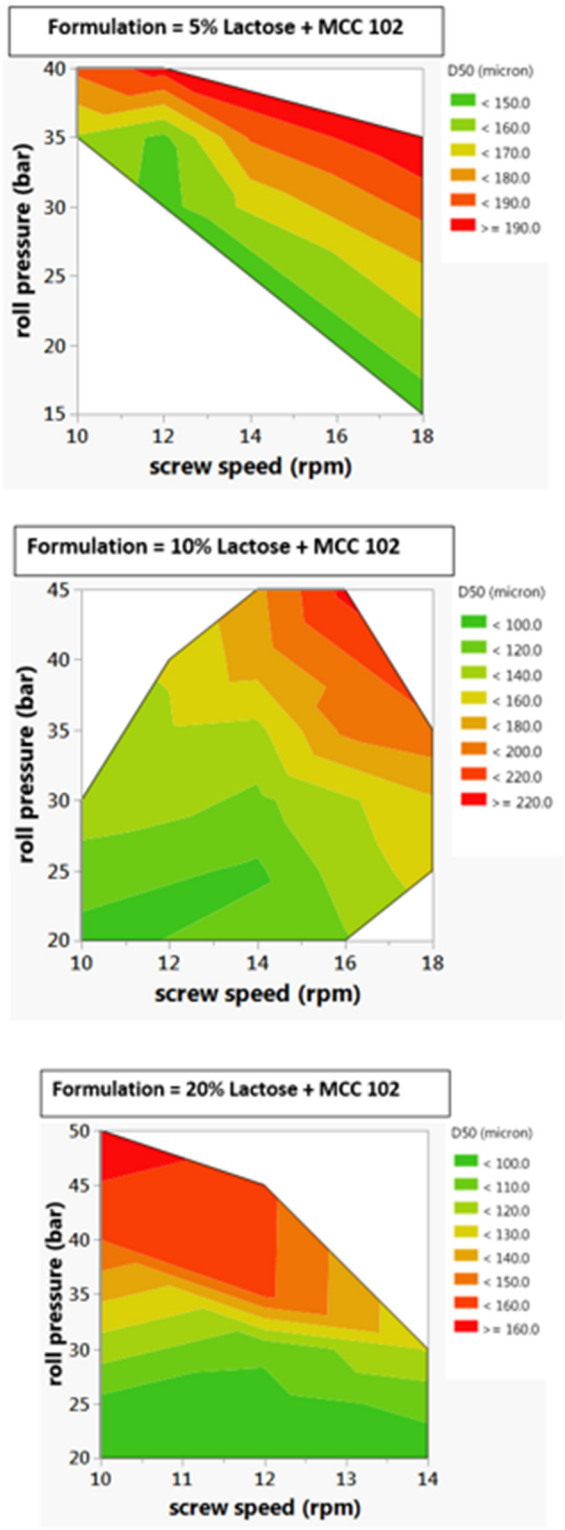


Figure 11. Contour plot for d50 of granules (microns), formulation=5, 10 and 20 wt. % lactose.

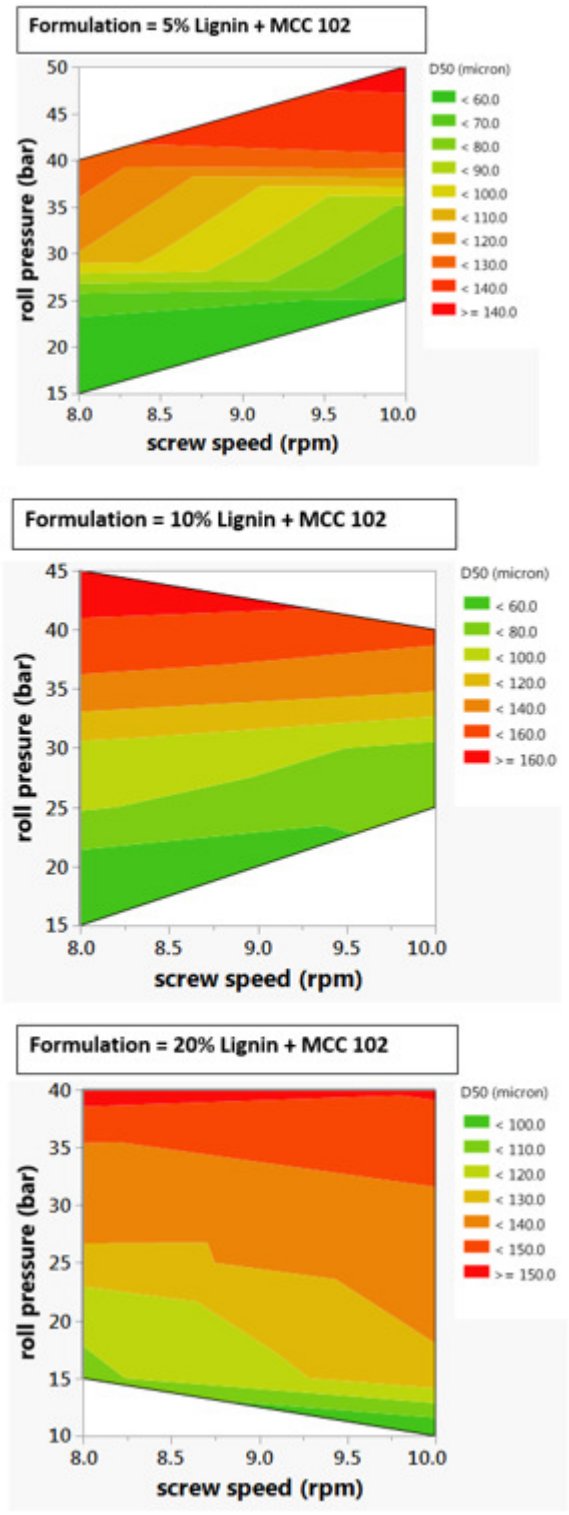


Figure 12. Contour plot for d50 of granules (microns), formulation=5, 10 and 20 wt. % Alcell lignin.

4. NIR spectroscopy

NIR spectroscopy was conducted to correlate the obtained spectra to the ribbon density obtained by roller compaction. The aim is to evaluate the applicability of NIR as a process analytical tool (PAT)

for development of continuous pharmaceutical manufacturing. The NIR spectroscopy has the ability to be used as on-line measurement tool of critical quality attributes of granules and ribbons such as density [21, 22, 24]. In order to evaluate the applicability of NIR for characterisation of various formulations and formulations containing lignin, the produced ribbons were characterised by a NIR probe to measure the envelope density. Off-line NIR spectroscopy was used by Multieye NIR instrument with the wavelength range of 1500-2200 nm and one probe to monitoring of Critical Quality Attributes. The NIR absorbance was found to be proportional to the envelope density of the ribbons. Partial Least Square (PLS) regression analysis was used for the calibration of the NIR results [22]. Cross validation analysis was conducted to calculate the numbers of principal components and the optimum number of components was obtained to be seven as shown in Figure 13. Utilising seven PLS components show more than 98 percent variance in ribbon density. However, considering higher PLS components may cause over-prediction, which is a major problem in estimation of ribbon density. Once the model has been built and calibrated, it can be used to measure the envelope density using the NIR spectra as inputs. The PLS regression results are shown in Fig. 14 where it can be concluded that the built PLS model is capable of calibrating the NIR spectrum to the density of the ribbons with an R-squared of 0.98 as shown in Figure 14.

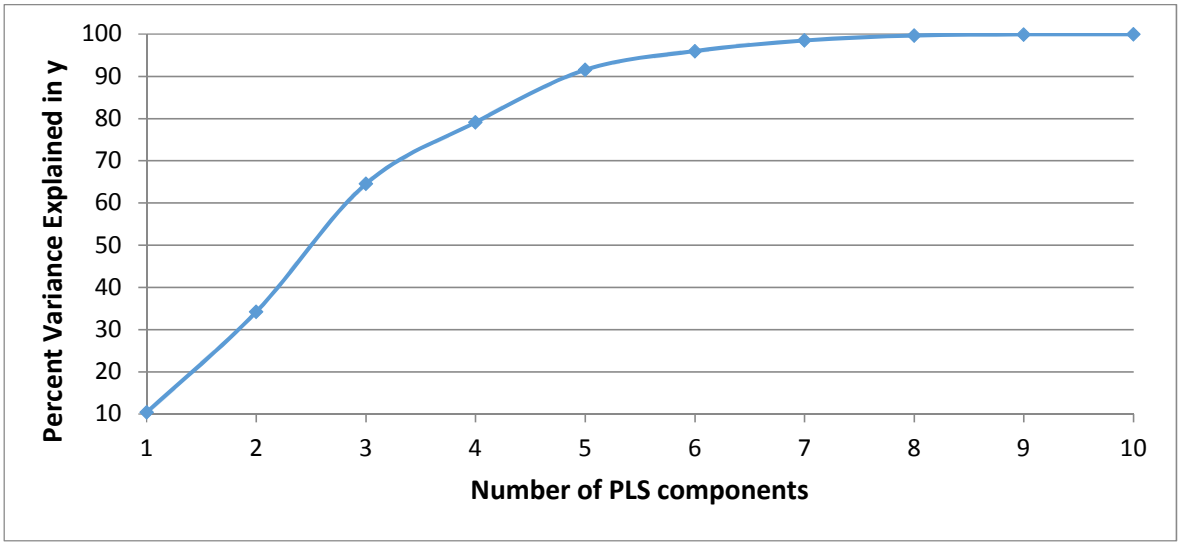


Figure 13. Percent of density variance explained versus number of PLS components.

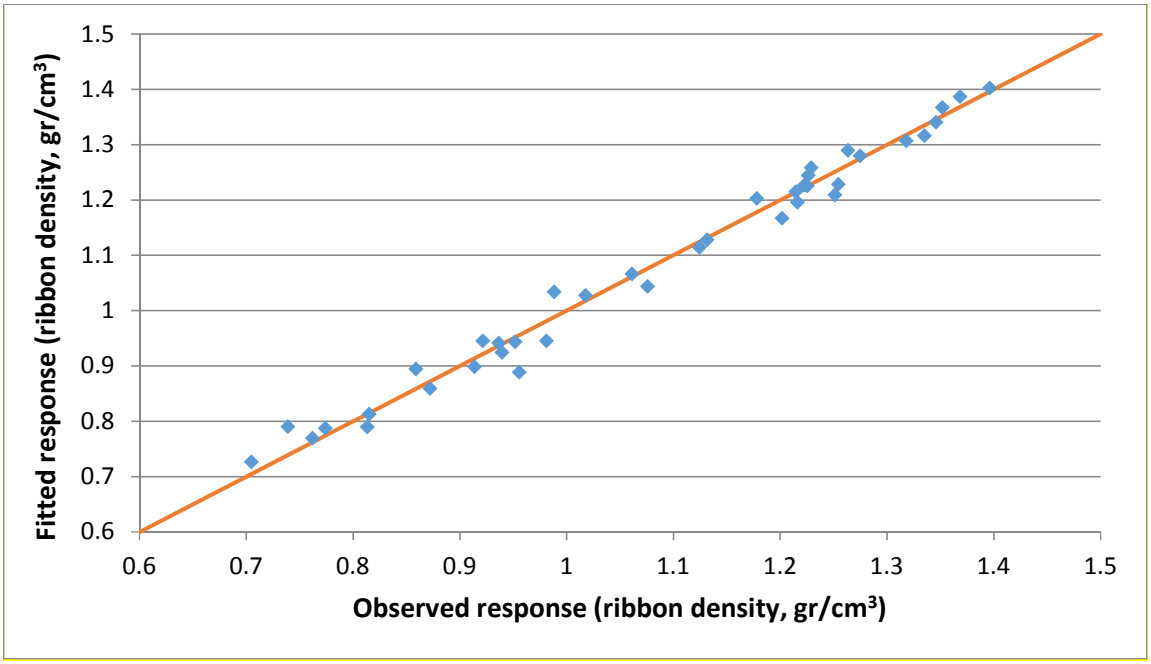


Figure 14. Predicted versus measured ribbon density calculated by NIR.

5. Conclusions

The main objective of this study was to implement the quality-by-design approach to identify the correlation between critical process parameters (CPPs) and critical quality attributes (CQAs) of outputs from a dry granulation by roller compaction process. A variety of excipients with differing formulations were prepared and used in roll compaction process to produce ribbons and granules. Microcrystalline cellulose (MCC 102) was used as the base excipient, as it is a common widely used material in dry granulation process due to its inherent properties such as good compressibility because of fibrous structure and high capacity. Other formulations containing lactose and Alcell lignin were considered to understand the influence of formulation on the CQAs.

The effects of CPPs including roll pressure and screw speed on the CQA, including ribbon density as well as D50 were investigated. The results indicated that a variation in roll pressure has a considerable effect on ribbon density and granules size (D50) in the roller compaction process. At higher roll pressure and constant screw speed, the amount of powder between rolls are constant and more pressure leads to more densification of powder, especially for smaller particle size, cohesive and compressible powders, and results in a higher density and larger D50 of granules size. On the other hand, it was found that screw speed does not have any significant effect on critical quality attributes

of products, and it affects other process variables such as the amount of powders, roll gap, and residence time of powders between rolls.

It was revealed that the properties and percentages of different excipients constrain the operability of the parameters used in roller compaction. However, as the process map is dependent on the formulation and equipment, generalisation of these process maps are needed based on dimensionless variables. The differences in mechanical properties of excipients leads to some differences in compaction behaviour during RC. Lactose shows higher compressibility than MCC 102 and Lignin. Therefore, lactose with smaller particle size, and larger surface area with increased particle contact tends to be more compressible than MCC 102, and can be used as modifier in the RC process. Also, lignin indicated almost similar behaviour with lactose, and can be a promising excipient in tablet manufacturing.

Another important objective of this study was to investigate the capability of Alcell lignin as natural polymer to use as excipient to improve powder properties, costs and delivery of tablets as final products. Alcell lignin, as a natural polymer can improve granulation process because of good flowability, low cost and ease of availability. Interestingly, it was revealed that less operational limitations was observed when lignin was introduced as an excipient in the formulations. Moreover, the applicability of NIR spectroscopy as PAT tool for on-line measurement of ribbon density in roller compaction process was investigated and NIR has been shown to be robust and reliable enough to be used as an on-line measurement in the RC process for formulations containing lignin.

Acknowledgements

This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750.

Appendix

A.1. Flow function

To measure the flowability of powders used in this study, the most commonly used parameter is flow function (FF) which is defined as [42, 43]:

$$FF=MPS/UYS \quad (A.1)$$

where MPS refers to the major principle stress acting on the powder, and UYS denotes the unconfined yield strength of the powder at the MPS. The values for MPS and UYS can be measured by shear cell test using FT4. The powders are categorised based on the FF values as listed in Table A.1.

Table A 1. Classification of powders based on FF values.

Type of flow	Flow function (FF)
Free flowing	FF > 10
Easy flowing	4<FF<10
Cohesive	2<FF<4
Very cohesive and non flowing	FF<2

A.2. Compressibility

Compressibility is a measure of how density changes as a function of applied normal stress. Indeed, compressibility is the ability of powder to reduce in volume by applying stress. For powders, the bulk property is influenced by many factors such as particle size distribution, cohesivity, particle shape, and particle surface texture. The standard measurement method for compressibility of powders utilises a vented piston to compress the sample under increasing normal stress, and the compressibility is calculated using the following equation:

$$\text{Compressibility} = \text{percentage change in volume after compression (\%)} \quad (A.2)$$

As we mentioned in the manuscript, the compressibility was measured by FT4 powder rheometer. For powders, density is a function of applied normal stress. The changes in density of powders as a function of applied normal stress are known as compressibility [44]:

$$Bulk\ Density = \frac{Split\ Mass}{Volume\ after\ Compression} \qquad \left(\frac{gr}{mL}\right) \tag{A.3}$$

$$Compressibility\ Index = \frac{Density\ after\ Compression}{Conditioned\ Bulk\ Density} \tag{A.4}$$

The compressibility of powders can be measured by using of Carr's index and Hausner Ratio [45]:

$$Compressiblity\ or\ Carr's\ Index\ Formula = 100 * \frac{(V0 - Vfinal)}{V0} \tag{A.5}$$

$$Hauner'sration = \frac{V0}{V} \tag{A.6}$$

The range of normal stress was between 1-2-4-6-8-10-12-15 kPa.

The Basic Flowability Energy (BFE) value were measured by FT4 powder rheometer for the materials and the results showed that MCC 102 has the highest value of BFE = 177 (MJ), this value indicates that this material is free-flowing. On the other hand, BFE of lactose was the lowest BFE= 81.1 mj, it means lactose is more cohesive than other materials and for Alcell lignin BFE = 119 mj.

A.3. Stability index

Stability index is a simple analysis carried out to understand whether the formulation being analysed changes during the analysis. It is an indication of the stability of formulation during characterisation. The stability test runs the formulation through a series of identical measurements, and similar results would be obtained if the formulation being tested is stable. If the stability index is approximately 1, it means the powder is physically stable. The SI >1 or SI < 1 shows unstable powder. FT4 powder analyser uses the following stability index formula [46, 47]:

$$Stability\ Index, SI = Energy\ Test\ 7 / Energy\ Test\ 1 \tag{A.7}$$

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In the first chapter, powder and granule characterization have been done for different excipients and lignin as a new excipient. The results were shown lignin can be used as excipient in tablet formulation. As per our satisfactory results, we decided to use lignin as excipient to study the effect of that on drug release rate. The advantages of using lignin are mentioned in our four chapters.

Chapter 2.

Effect of lignin on the release rate of acetylsalicylic acid tablets

International Journal of Biological Macromolecules
Volume 124, 1 March 2019, Pages 354-359

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Effect of lignin as natural polymer on the release rate of acetylsalicylic acid tablets

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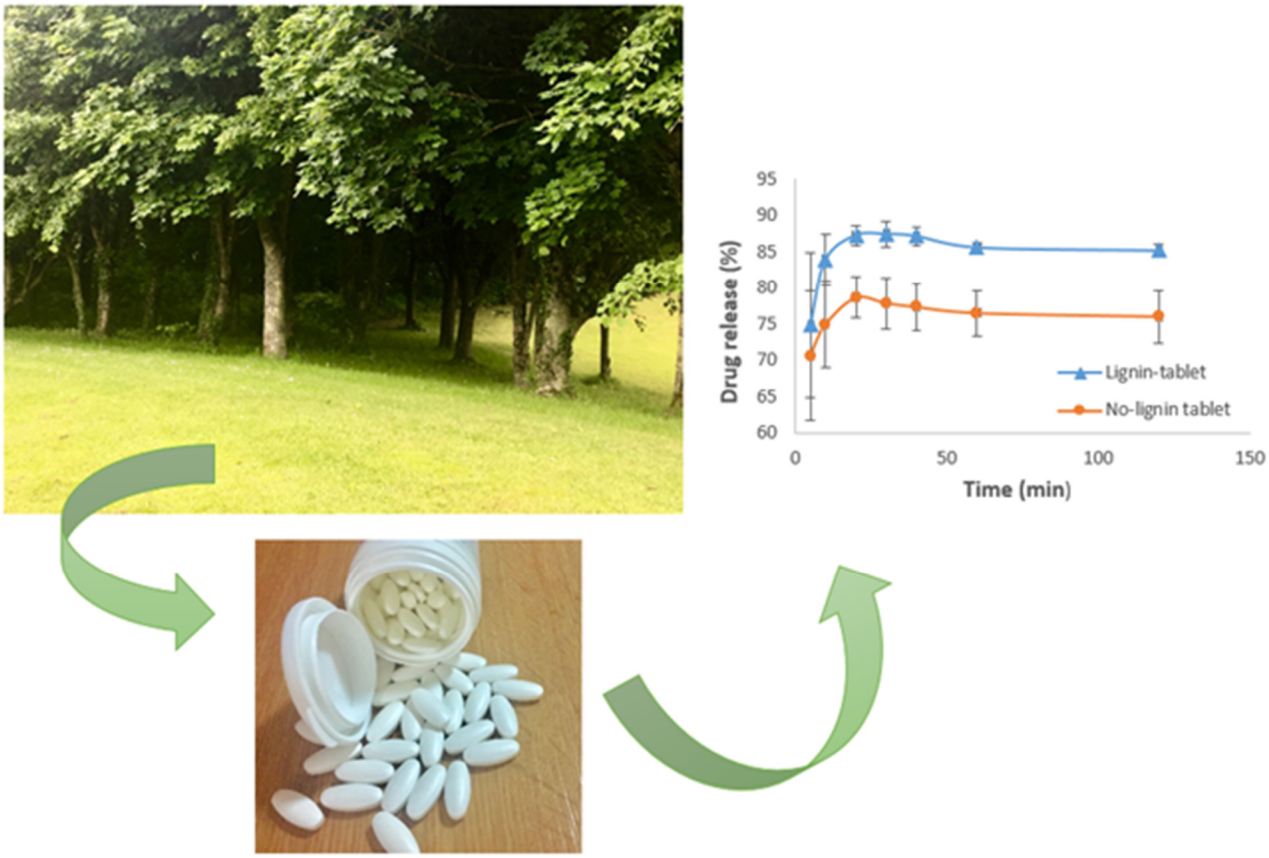
Abstract

The main focus here is on the improvement of formulations utilising non-conventional bio-based excipients to improve tablet release rates. Two different formulations were considered. The first formulation contains Alcell lignin, lactose monohydrate and microcrystalline cellulose as excipients and acetylsalicylic acid (aspirin) as active pharmaceutical ingredient (API). The second formulation contains lactose monohydrate and microcrystalline cellulose as excipients and aspirin as API. The prepared formulations were roller compacted followed by milling, sieving, and tableting. The tablets were then characterised in terms of dissolution rate in order to compare the release rates. Results indicated that tablets containing Alcell lignin have quicker release, faster disintegration times and higher tablet hardness for all samples with differing process parameters. Higher API dissolution has been attributed to the amorphous structure of lignin and its interaction with aspirin, which increases dissolution of the API.

Keywords: Lignin; Dry granulation; Roll compaction; Drug dissolution; Drug release; Hydrolysation; Acetylsalicylic acid

Graphical Abstract



1. Introduction

Three different methods are considered for tablet manufacturing in the pharmaceutical industry, i.e. direct compaction, dry, and wet granulation. Recently, there has been focus on direct compaction due to cost and time effectiveness as less number of processing steps are involved. Moreover, the tablets produced by direct compaction have faster dissolution rates [1]. However, in order to improve powder flowability and bulk density, especially for poor flowing materials, granulation has proved useful. Dry granulation is continuous and is the preferred method for moisture and heat sensitive materials as no binder is used [2-6].

Today, one of the major challenges facing the pharmaceutical industry is to enhance the bioavailability which play a crucial role in drug development [7]. Tablet release rate has a significant effect on tablet bioavailability [8] in which higher release rates result in higher bioavailability and lower side effects. Currently, the most common method for enhancing the bioavailability of drugs is preparation of amorphous solid dispersion. In an amorphous solid dispersion (ASD), the API is transformed to amorphous phase from crystalline by various techniques, and then API is dispersed in a polymeric carrier, which enhances the dissolution of API molecules.

Excipients are inert substances used in drug production to assist manufacturing and control the dosage, quality, stability, bioavailability, toxicity and efficacy [9-11]. For example, sugar compounds such as lactose and cellulose derivatives such as MCC are the most commonly used excipients in tablet manufacturing [10, 12, 13]. In this study, in order to investigate the effect of excipient on tablet release rate, disintegration and dissolution tests have been extensively studied [14-17]. Several researchers have illustrated that the influence of excipients on release of oral dosage drugs is significant [18-20]. The type of excipient, its physical and chemical properties, and interaction with API can effect processability and stability of tablets as well as overcome the drug side effects [21]. Therefore, tablet formulation can be considered as a critical factor in pharmaceutical production due to its considerable effect on disintegration, dissolution and drug release rate [7, 20, 22-24].

Various researchers have focused on improved tablet release rate and drug absorption, etc. by developing novel excipients. Due to some issues in relation to side effects and release rates of solid dosage forms [25], use of materials with desired functionality as excipient in tablets are increasing. In tablet manufacturing, amorphous materials are showing great promise as excipients as they exhibit higher dissolution compared to crystalline equivalents due to disordered structure and higher free energy [25-29]. On the other hand, the thermodynamic instability of amorphous excipients used in tablets, might result in relaxation and crystal growth of crystalline API molecules over time which is not favourable for bioavailability [30].

Recently, biological macromolecules have attracted attention for use as excipient in tablet production to enhance drug dissolution and bioavailability. A number of studies have been carried out on lignin to improve chemical modification [31-33], and to develop new pharmaceutical formulations with increased functionality [34, 35] because of lignin structure which contains phenolic and aliphatic hydroxyl groups [35]. Lignin has a high potential to be used in tablet manufacturing either with chemical modification or without chemical modification [32]. Furthermore, some researchers have investigated the ability of lignin's nanoparticles (NPs) in drug delivery due to its non-toxicity, biodegradability and stability. Lignin has also been used to transport hydrophobic drugs [36]. Lignin is an amorphous polymer and non-amphiphilic in nature, and displays high chemical stability due to 3D network structure [37]. As lignin is rich in phenolic and aliphatic hydroxyl groups [38], it interacts with most API molecules through π-π stacking and hydrogen bonding, and this makes lignin potentially useful as a drug carrier to enhance bioavailability [39-42].

Aspirin, which is known as a delayed-release drug is utilised as a model API in this work [43, 44]. In fact, the dissolution rate of aspirin is the rate-limiting step, which controls the absorption and bioavailability. Moreover, another challenge associated with aspirin is that it hydrolyses to salicylic acid upon exposure to aqueous solutions, which should be taken into account during the dissolution tests [8, 15, 41, 45-47]. Wang et al. have investigated aspirin hydrolysis during dissolution tests, and

found out that the hydrolysis of aspirin occurs during dissolution [47]. Sumirtapura et al. studied the dissolution of different types of acetylsalicylic acid products, and distinguished time lags for differing aspirin tablets [46]. Peltonen et al. utilised three different tablets containing aspirin for dissolution tests. The first type of tablets contained aspirin and MCC; the second ones consisted of aspirin and lactose, while the third ones included aspirin, lactose and MCC. They investigated the effect of pH on aspirin release rate and found higher release at higher pH. Moreover, they reported that adding lactose to aspirin in the formulation leads to increased release rate. On the other hand, adding MCC results in decreased release rate [15].

In comparison with other literature, the authors have tried to analyse the dissolution of different formulations containing aspirin as API and various excipients. Lignin was used as a new excipient to evaluate its performance in tablet manufacturing in order to improve drug release rates. Indeed, the purpose of this study is to investigate the effect of Alcell lignin on tablet properties including hardness, disintegration time and drug release rate. The main aim is to explore the possibility of using lignin as natural material to enhance bioavailability of poorly water-soluble drugs. Two different formulations are utilised, one formulation containing Alcell lignin and another one without lignin. First, two different blends are roller compacted to produce ribbons. Then, the produced ribbons are milled to make granules. Afterwards, these granules are used to produce tablets. Different tablet characterisation tests including; disintegration, hardness and dissolution tests are carried out to understand the effect of lignin as natural polymer on drug release rate.

2. Experimental procedure

2.1. Materials and methods

In order to prepare the formulations, acetylsalicylic acid (Alfa Aesar, 99% $C_9H_8O_4$) was utilised as a model API. Different excipients were utilised including microcrystalline cellulose (MCC SANAQ® 102 L USP/NF/EP), lactose monohydrate (Lennox USP, NF, BP, Ph, pure pharma grade) and Alcell lignin (Tecnaro (Ilsfeld, Germany)). More details on the lignin used in this study can be found elsewhere [33, 48]. To prepare the mixtures, 1% w/w magnesium stearate (Sigma-Aldrich, Ph. Eur.,

BP, ≥90% stearic and palmitic acid basis), as lubricant and croscarmellose sodium (CCS) (IMCD NF, PH.Eur.,JP) as disintegrant were used in the formulations. Table 1 illustrates the two different formulations considered; in the first one; 5 wt. % of aspirin was mixed with 20 wt. % of lactose, 20 wt. % of lignin, 3 wt. % of CCS and 1 wt. % MgSt, and the rest is MCC 102. The second formulation was prepared with 5 wt. % of aspirin, 20 wt. % of lactose, 3 wt. % of CCS, 1 wt. % MgSt, and the rest is MCC 102. All components were mixed using a Morphy Richards Stand Mixer. Ortho-phosphoric acid (analytical reagent grade, Fisher Scientific UK) and acetonitrile, HPLC grade, 99.7+% min Liquid (Alfa Aesar) were mixed to prepare mobile phase for HPLC analysis.

Table 1. Characteristics of different formulations used in this study.

Material	A	B
Acetylsalicylic acid (% wt.)	5	5
Alcell lignin (% wt.)	20	0
Lactose (% wt.)	20	20
MCC 102 (% wt.)	51	71
Croscarmellose sodium (% wt.)	3	3
Magnesium stearate (% wt.)	1	1

2.2. Equipment and instruments

2.2.1 Dry granulation by roll compaction and milling process

To prepare the tablets, the dry granulation method was used for the entirety of this work in a series of ribbon production, milling, and tabletting. The ribbons were produced using a roller compactor (Freund TF-MINI, Vector Corporation, Japan) integrated with a vertical screw feeder for feeding the formulations. The rollers dimensions are 100 mm in diameter and 25 mm in width. The considered process parameters included screw speed (SS) and roll pressure (RP), while roll speed was kept constant at 4 rpm. The screw speed was changed between 10-14 rpm, and roll pressure was changed between 30-50 bars in the ribbon production experiments. The density of produced ribbons were measured using GeoPyc density analyser (GeoPyc 1360, Micrometrics Instrument Corp. 4356 communications Drive, Norcross, GA 30093, USA). The produced ribbons were then milled using a

conical mill (Laboratory Comil 193 AS, Quadro, USA) with mesh size of 813 µm, and impeller speed of 3000 rpm. The particle size distribution (PSD) of fine powder and granules were measured using Microtrac S3500 particle size analyser (Malvern, USA).

2.2.2 Tablet preparation and characterisation

A benchtop single punch tablet press (Gamlen Tableting GTD-1 D series, UK) was used to produce the tablets with different formulations. 100 mg of two different formulations of produced granules were pressed to make tablets in a 6 mm (diameter) die. The tablet compression was carried out at 180 mm/min speed under fixed load of 400 kg. Croscarmellose sodium was used as super disintegrant in tablet preparation experiments [23].

Hardness of the produced tablets was measured using a tablet hardness tester (Pharma Test, PTB 311E 3 in 1 hardness, diameter and thickness tester, Hainburg, Germany).. To measure the disintegration time, Pharma Test PTZ-DIST- Disintegration Test Instrument (Hainburg, Germany) was used. The apparatus chamber was filled with 900 mL of deionized water and the apparatus paddle was adjusted at 100 rpm. Three samples were tested in deionized water at 37˚C for each process parameters and for two different formulations. All the disintegration tests were conducted until the tablets completely disintegrate. The dissolution of produced tablets was performed using a Pharma Test PTWS 120D 6-Station Tablet Dissolution Testing Instrument (Hainburg, Germany).

The concentration of the API in each sample was measured using High Performance Liquid Chromatography (HPLC). Chromatography was performed using an Agilent Technologies (Waldbron, Germany) 1260 Infinity II HPLC system. The HPLC system consisted of a quaternary pump G1311B, a diode array detector G1315D set at wavelengths of 200 nm for acetylsalicylic acid and salicylic acid, auto-sampler G1329 B and a thermostated column compartment G1316A set at 25 ˚C. The system operated under isocratic flow at 0.75 mL/min using mobile phases consisting of A) 0.1 % Ortho-phosphoric acid; B) acetonitrile; A/B =50/50, v/v. The injection volume was 10 mL. The total run time was 10 minutes, and the type of column used was Kromasil 5C18 (250×4.6 mm).

2.3. Dissolution test procedure

The dissolution chamber was filled with 500 mL of prepared medium 0.1 N HCl (ACS, ISO, Reag. Ph Eur, Hydrochloric acid fuming 37% wt.) at pH=1.2. The medium temperature was kept constant at 37 ± 0.5˚C and the stirrer was adjusted to a speed of 75 rpm [45]. When the temperature reached 37˚C, one tablet was placed in each dissolution vessel to run the dissolution test for 120 minutes. Three mL of the dissolution medium were withdrawn at 5, 10, 20, 30, 40, 50, 60 and 120 minutes, then medium was replaced with the same amount, immediately. Then, the samples were filtered using Captiva Econofilters (PTFE membrane, 13 mm diameter, 0.2-µm pore size) syringes to prepare for the analysis by HPLC at 200 nm wavelength, immediately, due to hydrolysis of acetylsalicylic acid.

In order to prepare the buffer solution (pH = 1.2) for the dissolution tests, 2 g sodium chloride was dissolved in 200 mL deionized water. Then, it was diluted with deionized water in a 1000 mL volumetric flask and 7 mL HCl was added. In order to prepare the calibration solutions for HPLC analysis, 5 mg of acetylsalicylic acid and 5 mg salicylic acid were dissolved in 20 mL of buffer solution, separately. Then, they were mixed to prepare the calibration solution. Afterwards, the prepared solutions were diluted with buffer solution 6 times. The standard curves of drug concentration vs peak area were drawn for different formulations giving R^2= 0.99.

3. Results and discussion

3.1. Dissolution profiles for two different formulations

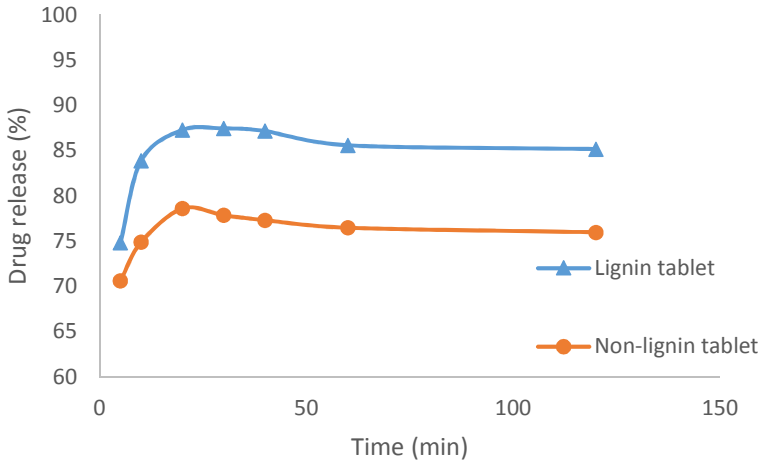
Two different formulations were evaluated to find the effect of Alcell lignin on the aspirin tablet release rate. One formulation contains Alcell lignin, MCC 102 and lactose as excipients and the other one contains lactose and MCC 102 as excipients. Both formulations contain aspirin as API. Fig. 1 illustrates the graphs of drug release rate for tablets prepared at various process parameters. As seen, different levels of screw speed and roll pressure were considered in this study. Interestingly, the results show that the tablets containing Alcell lignin have higher release rate than the tablets without lignin for all prepared samples. In addition, the equilibrium dissolution for the tablets containing lignin is greater which is attributed to the enhancement of solubility of ASA with addition of lignin. It is also seen that faster release kinetics is obtained for the tablets containing lignin such that the

majority of the API are dissolved in the first 10 minutes of the dissolution test. Moreover, the tablets prepared with lignin indicated less variability in the dissolution measurements. The data is provided in the Supplementary file for both formulations.

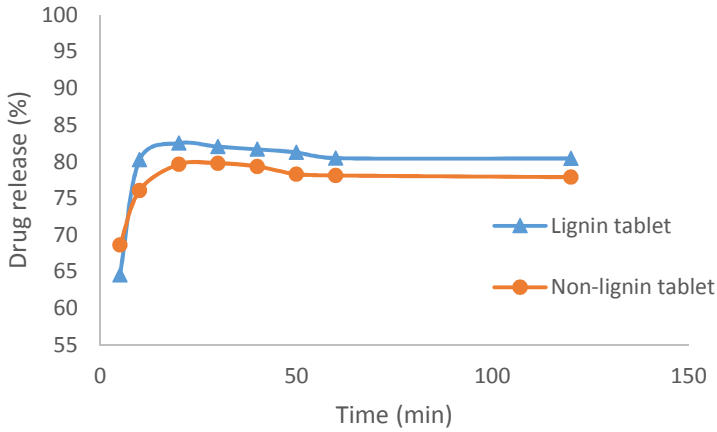
In other words, tablets containing lignin with very high release rate acts as a disintegrating agent in the dissolution chamber, facilitate the dissolution kinetics, and accelerate to equilibrium release. Moreover, due to amorphous nature of lignin, it may be concluded that lignin enhances the solubility of API due to its disordered structure and higher Gibbs free energy of the amorphous phase in the dissolution media. The cross-linked structure of lignin is likely to have an effect on dissolution and disintegration as well. Peltonen et al. [15] studied the effect of pH on the release rate of aspirin tablets with different formulations (B (aspirin & lactose), A (aspirin, lactose &MCC) and C (aspirin &MCC)). They illustrated in pH 1.2 the release rate of aspirin with the different formulations are low and it does not show 100% release rate after more than 200 minutes. Maximum release rates of the formulation B was around 90% after 200 minutes. For formulation A, the release rate was around 80% after 500 minutes and for formulation C was around 70% after 500 minutes.

The roll compaction process parameters affect the release rate of aspirin also in which the effect of roll pressure is more significant compared to screw speed. For the tablets without lignin, increasing roll pressure (at constant screw speed of 14 rpm) results in reduction of API dissolution, which could be attributed to the particle size of granules, which produce the tablets. In the roll compaction process, increasing the roll pressure results in enhancement of granule size. However, the effect of process parameters on the API dissolution is not significant, because the dissolution depends mainly on the chemical structure of API and interaction with the dissolution medium. In fact, the granulation improves the flowability of particles in the manufacturing.

Screw speed=14 rpm- Roll pressure=30 bar



Screw speed=14 rpm- Roll pressure=40 bar



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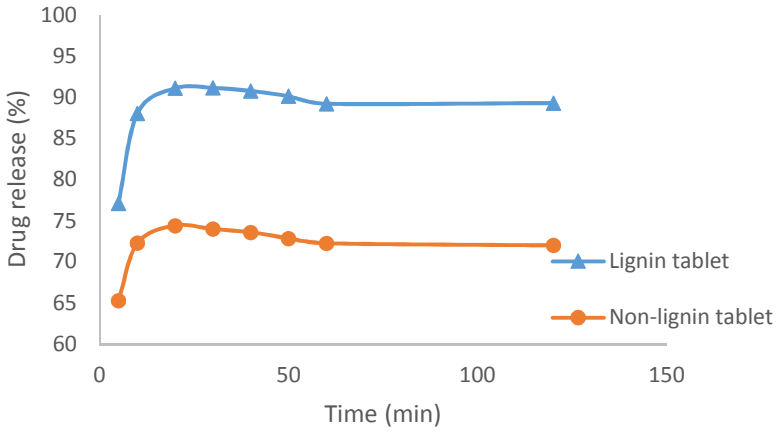
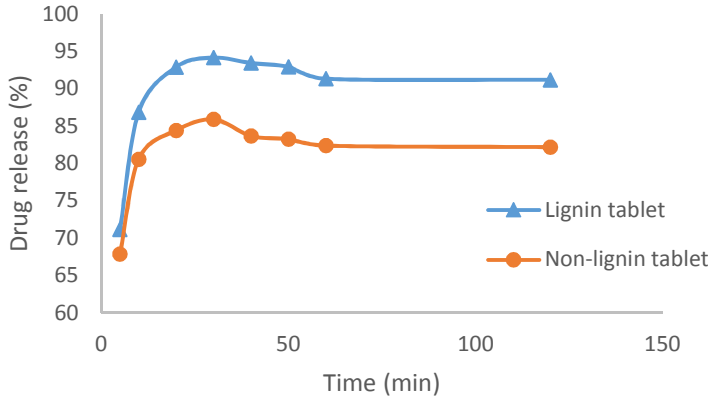
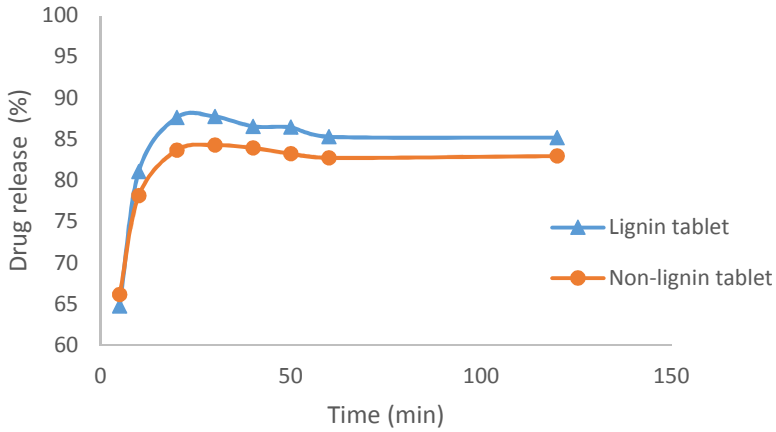


Screw speed=12 rpm- Roll pressure=30 bar



Screw speed=12 rpm-Roll pressure=40 bar



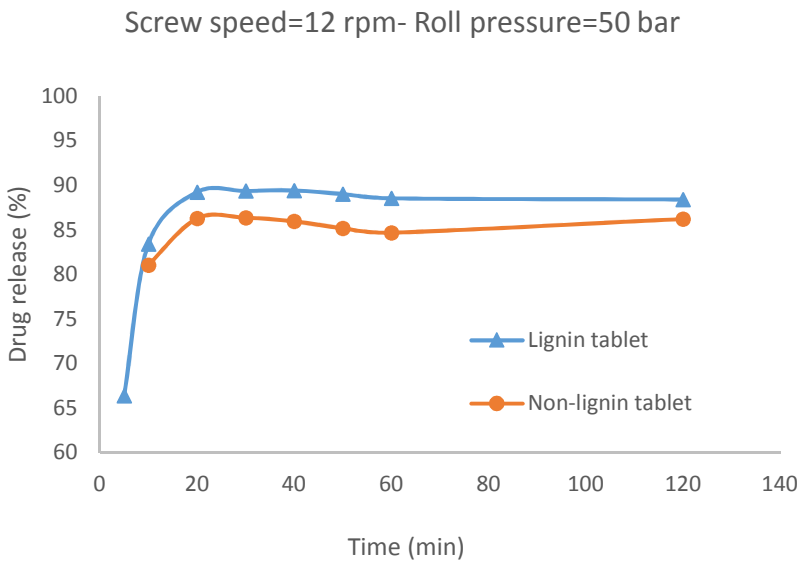


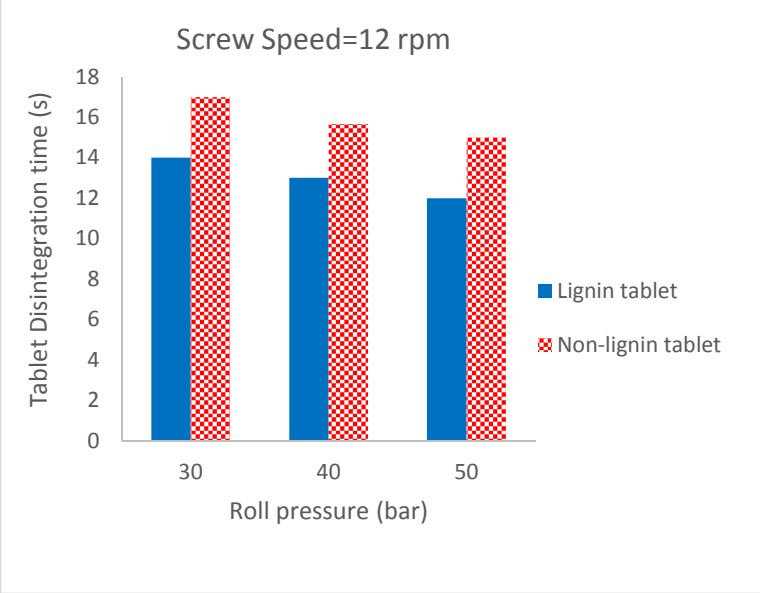
Figure 1. Dissolution release rate of acetylsalicylic acid for different lignin and non-lignin tablets at different process parameters.

3.2. Effect of process parameters on tablet disintegration time

The effect of roll pressure and screw speed as the main process parameters of dry granulation on the tablet disintegration time for the two formulations is shown in Fig. 2. In terms of the effect of roll pressure as process parameter on disintegration time of tablets, the results illustrate that increasing the roll pressure while keeping the screw speed constant, results in decreasing the disintegration time for both formulations. Increasing the roll pressure results in higher densify of ribbons during the roll compaction process, and subsequently produce larger granules because higher mechanical energy is required to break up the ribbons during the milling step. The tablets made with larger granules will be more porous, and subsequently leads to faster disintegration time. It is also observed from Fig. 2 that the tablets containing lignin have faster disintegration time than non-lignin tablets due to the amorphous and inherent structure of lignin, which has higher affinity towards the solution media compared to MCC and lactose.

Moreover, the particle size of raw materials used as excipients are shown in Fig. 3. As observed, lignin has smaller particle size compared to MCC 102, and introducing lignin as an excipient results in better compaction behaviour. In fact, smaller particles provide better particle-particle contact

during the roll compaction and denser ribbons are produced, which in turn results in larger granules in the milling stage [49]. Furthermore, the size distributions of the used granules for tableting are shown in the Supplementary file. It is seen that the formulation containing lignin has slightly larger granule size, which results in faster disintegration time.



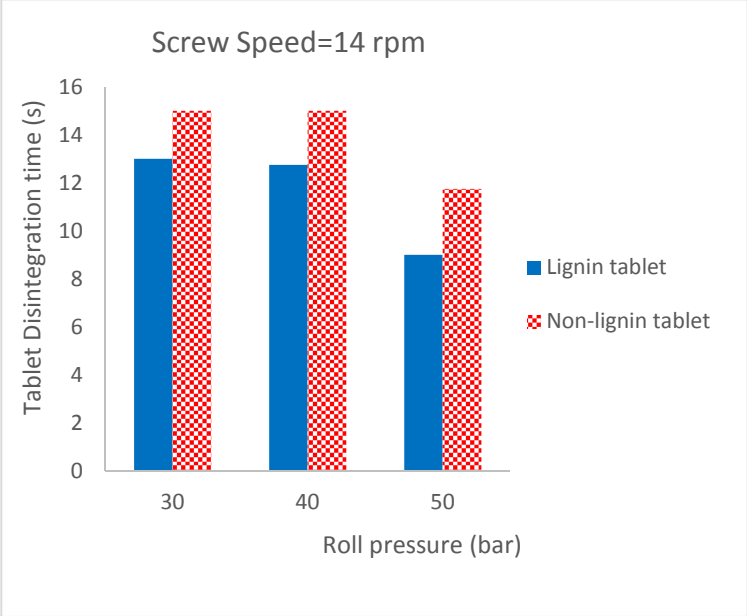


Figure 2. Disintegration time of tablets prepared with and without lignin as function of process parameters.

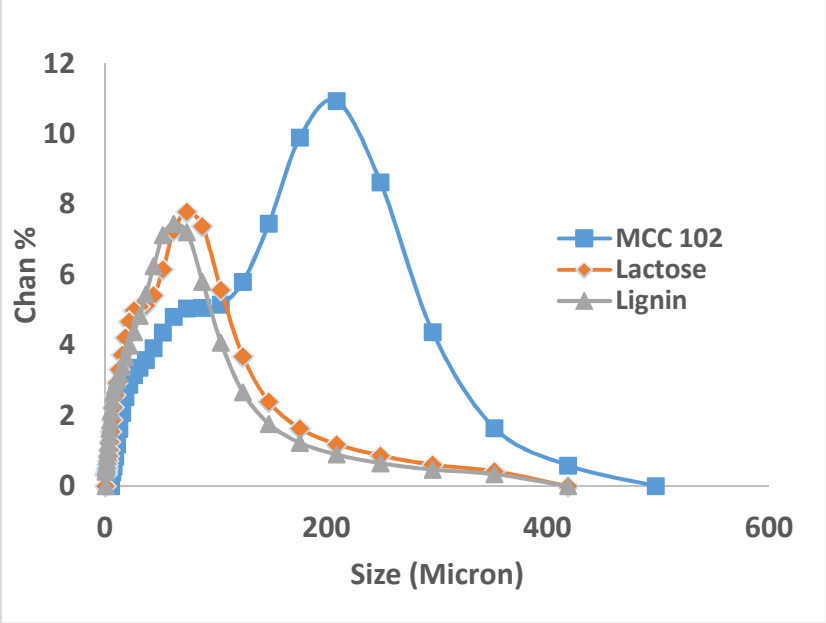


Figure 3. Particle size distribution of materials; MCC 102, lactose and lignin.

3.3. Effect of process parameters on tablet hardness

Fig. 4 illustrates the hardness of the tablets prepared using the two formulations as a function of process parameters. The results reveal that the lignin tablets have higher hardness than non-lignin tablets for all samples. Also, it can be seen that increasing the roll pressure leads to reduction of tablet

hardness due to larger granules being obtained at higher roll pressure which in turn leads to weak physical bonds between particles. The results also indicate that by increasing screw speed, the tablet hardness decreases; however, the change is not considerable. In addition, the standard range of tablet hardness is between 39-79 N, therefore the lignin tablets are within the standard range of hardness. The reason why tablets containing lignin display higher hardness can be attributed to the interaction between lignin and other constituents of the formulation where lignin acts as a binder thereby increasing tablet hardness.

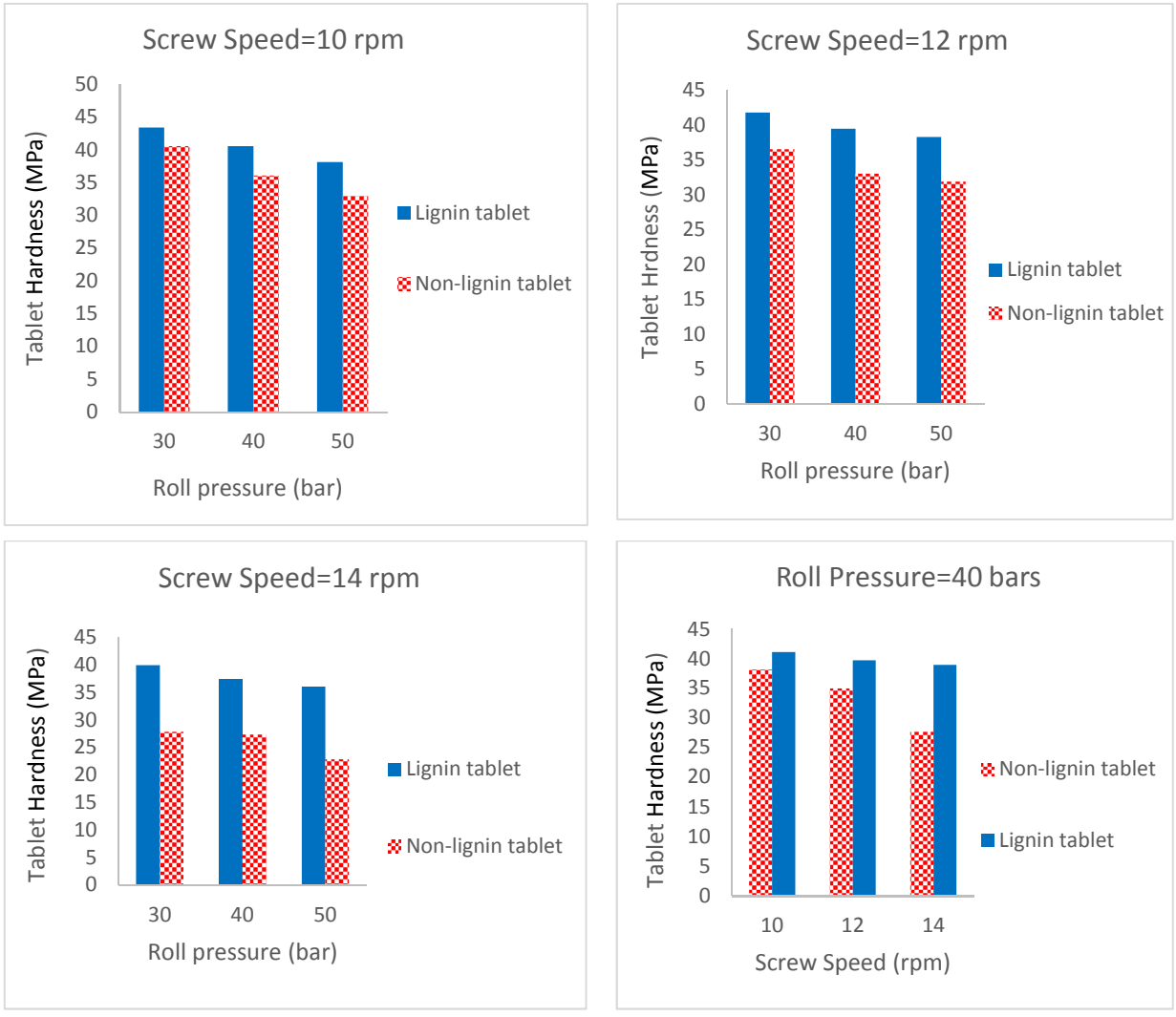


Figure 4. Hardness of tablets prepared with and without lignin as function of process parameters.

4. Conclusions

The main aim of this study was to investigate the effect of lignin-based excipients on release of oral dosage aspirin tablets. Lignin was selected as an excipient to evaluate its influence on release rate and tablet properties at varying processing conditions due its chemical structure. Results illustrated that lignin tablets compared to non-lignin tablets have higher hardness, faster disintegration time, and higher release rate. Indeed, the critical quality attributes of the tablets were improved by introducing the lignin. Higher release rate of tablets with lignin formulation are due to amorphous structure of lignin and interaction with the API, which improves drug solubility and therefore bioavailability, the key factor in oral dosage development. On the other hand, higher roll pressure leads to more densified ribbons associated with lignin blends and consequently, larger granules are produced. These larger granules result in porous tablets, which leads to faster disintegration times as solute diffuses faster into the tablets. Also, the greater hardness for the tablets containing lignin are attributed to better affinity between lignin and MCC which leads to lignin acting as a tablet binder.

Acknowledgements

This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750.

The authors also would like to thank Dr. Ali Sheikhi, Department of Mathematics, University of Limerick, for his useful comments on the statistical analysis.

Supplementary file

The results pertaining to granule size distribution as well as variability of the dissolution tests and t-test results can be found in the supplementary file online at **www.sciencedirect.com**. A paired-samples t-test was performed to assess the difference between release rate of two different type of tablets, without lignin and with lignin.

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Supplementary file

Effect of lignin as natural polymer on the release rate of acetylsalicylic acid tablets

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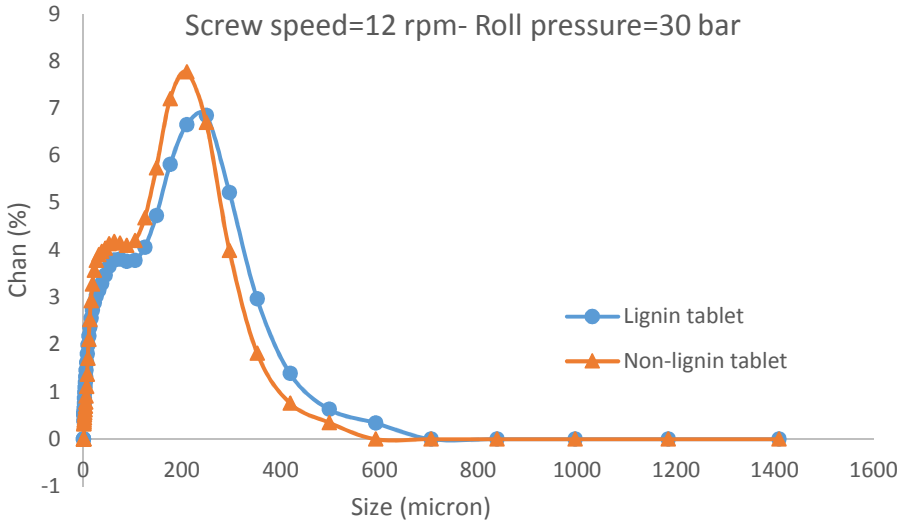
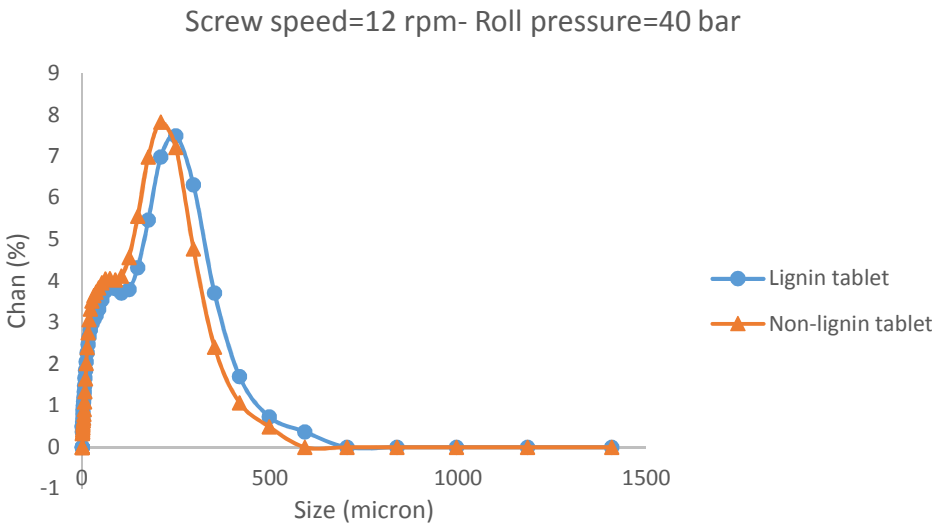
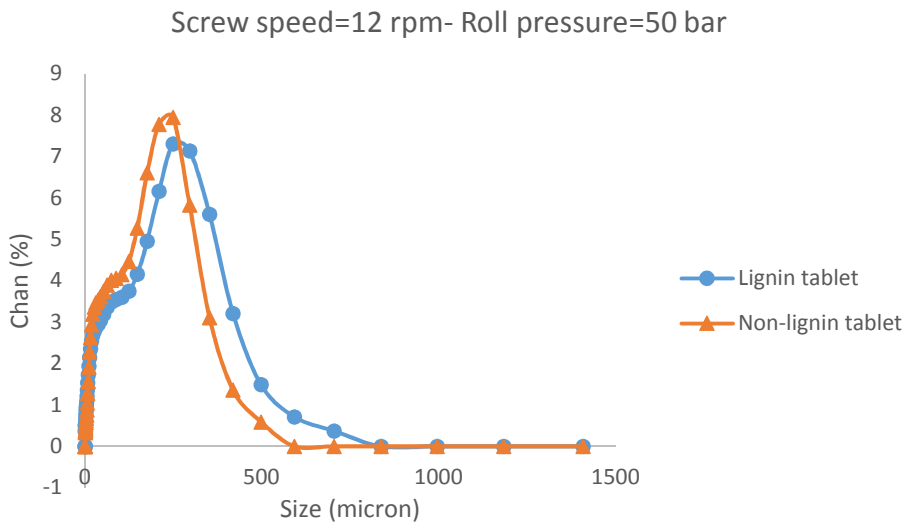
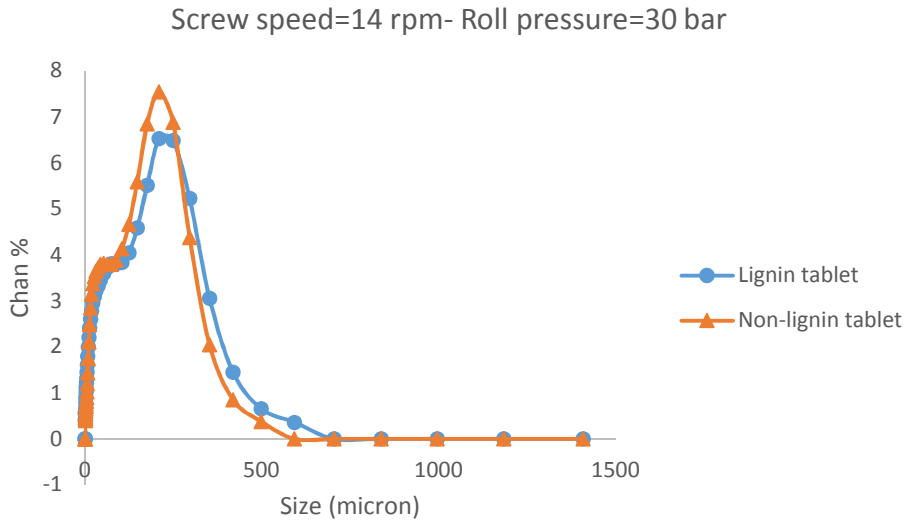
1. Granule size distribution

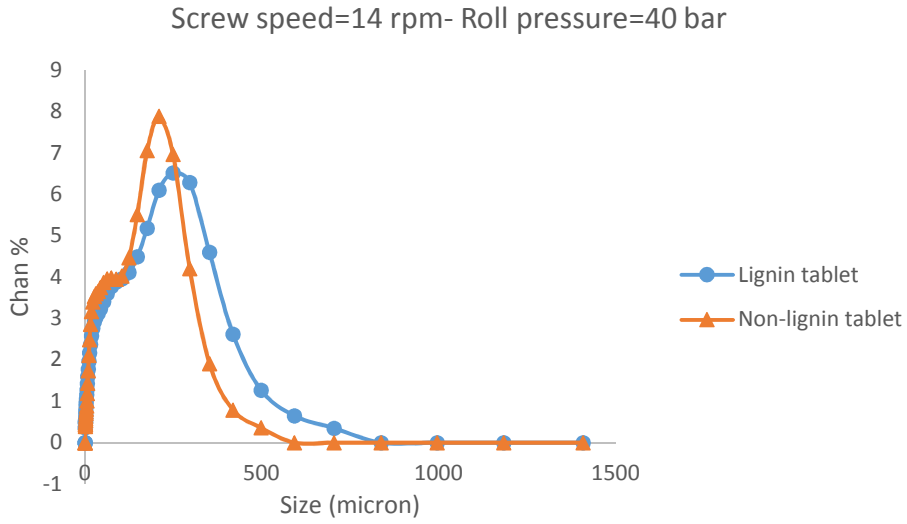
Granule size distribution of the prepared granules at various conditions are presented in Figure S1.






Screw speed=12 rpm- Roll pressure=50 bar
Chan (%)
9
8
7
6
5
4
3
2
1
0
-1
0
500
1000
1500
Size (micron)
Lignin tablet
Non-lignin tablet


Screw speed=14 rpm- Roll pressure=30 bar
Chan %
8
7
6
5
4
3
2
1
0
-1
0
500
1000
1500
Size (micron)
Lignin tablet
Non-lignin tablet


Screw speed=14 rpm- Roll pressure=40 bar
Chan %
9
8
7
6
5
4
3
2
1
0
-1
0
500
1000
1500
Size (micron)
Lignin tablet
Non-lignin tablet

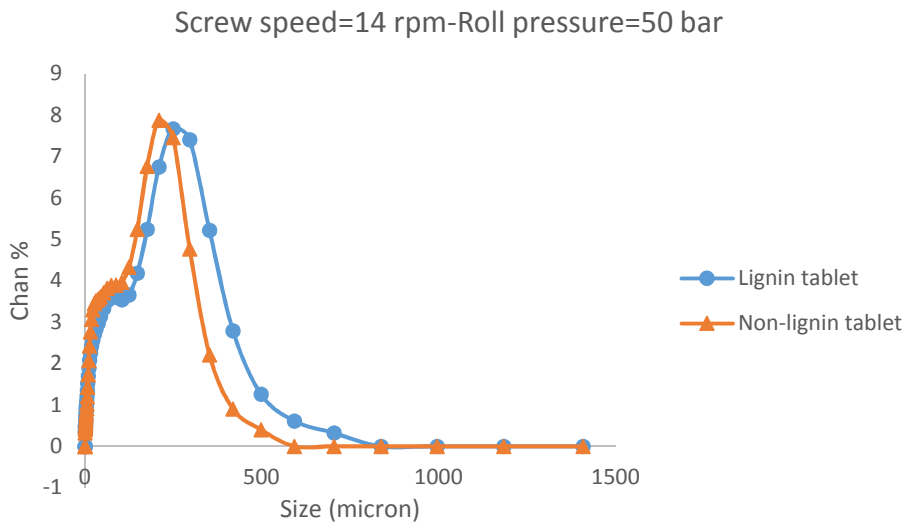
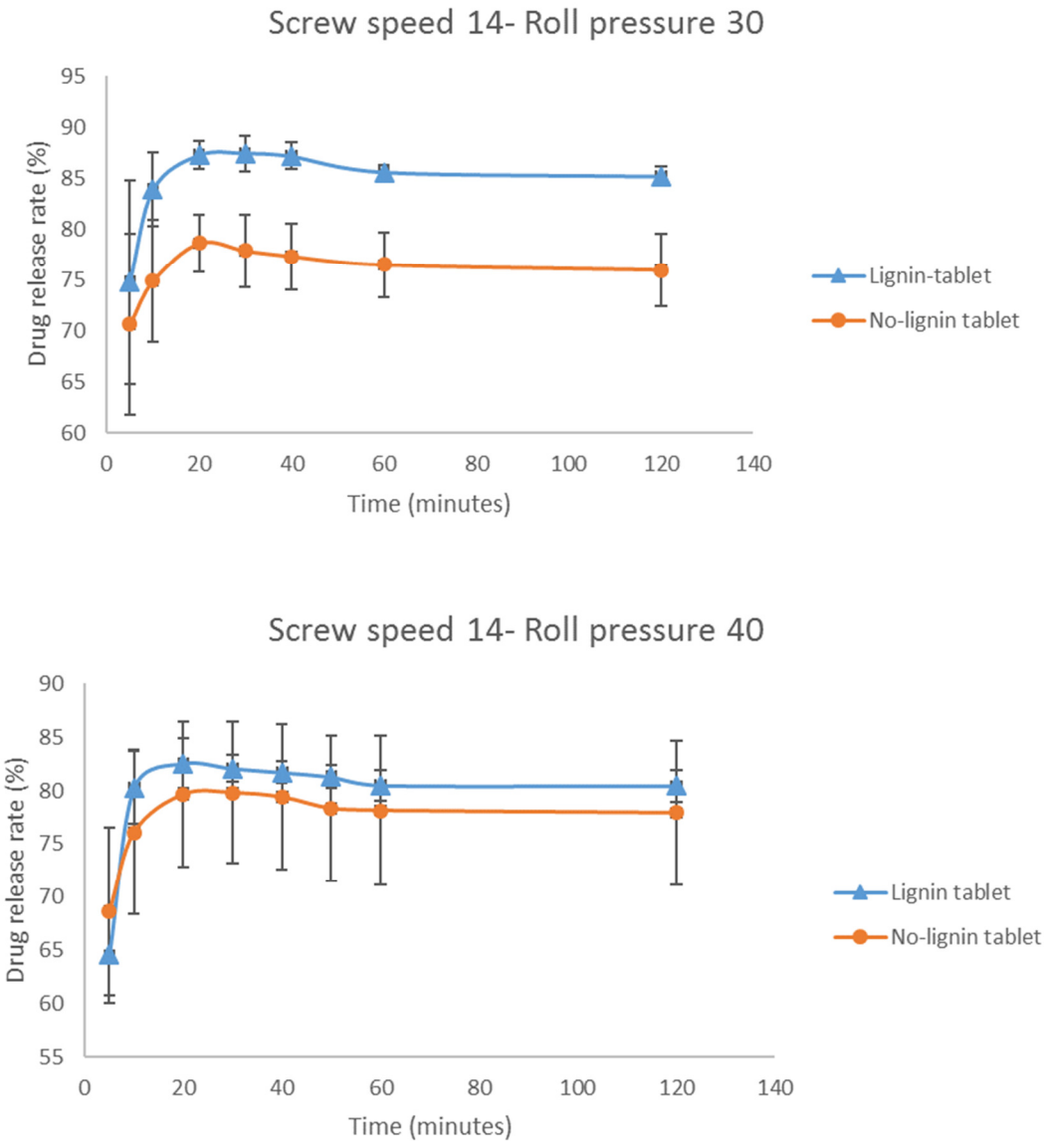


Figure S1: Particle size distribution of granules obtained at different process parameters.

2. Statistical analysis and Error bars

The variability of tablet dissolution tests are shown in Figure S2 as the error bar for lignin formulation as well as non-lignin formulation.



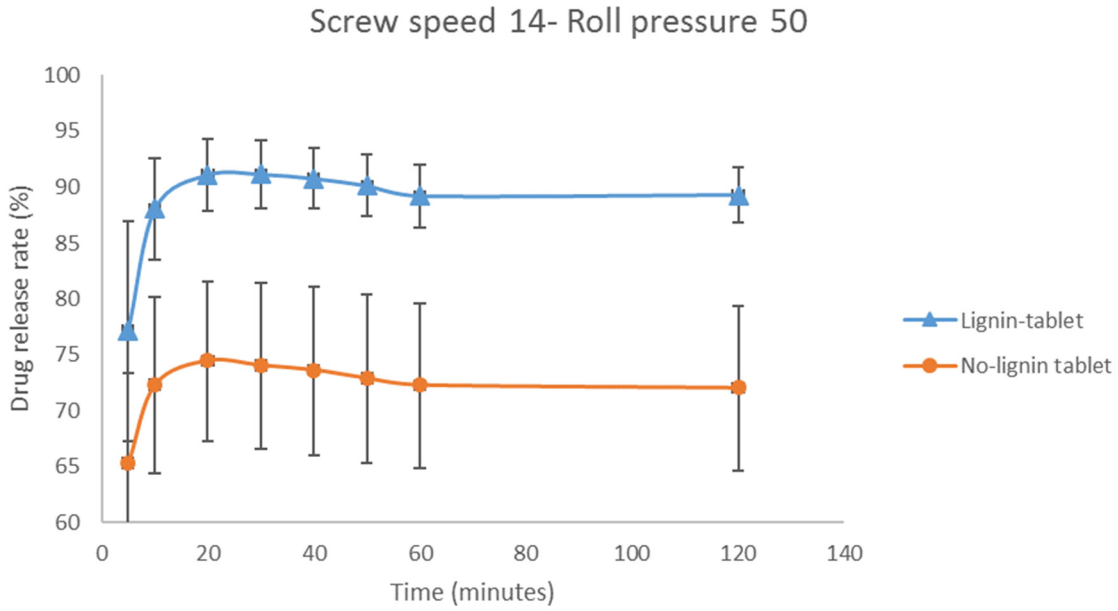
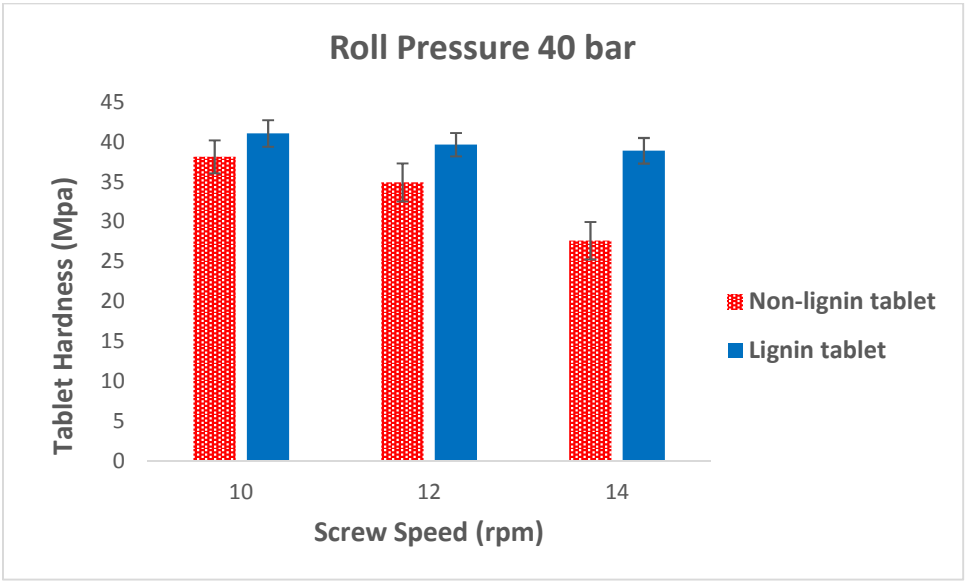
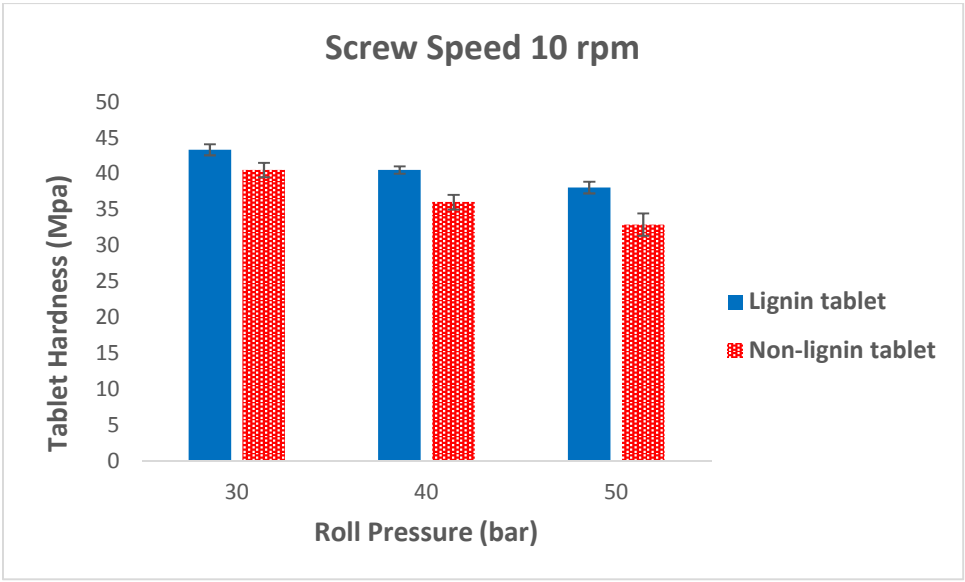
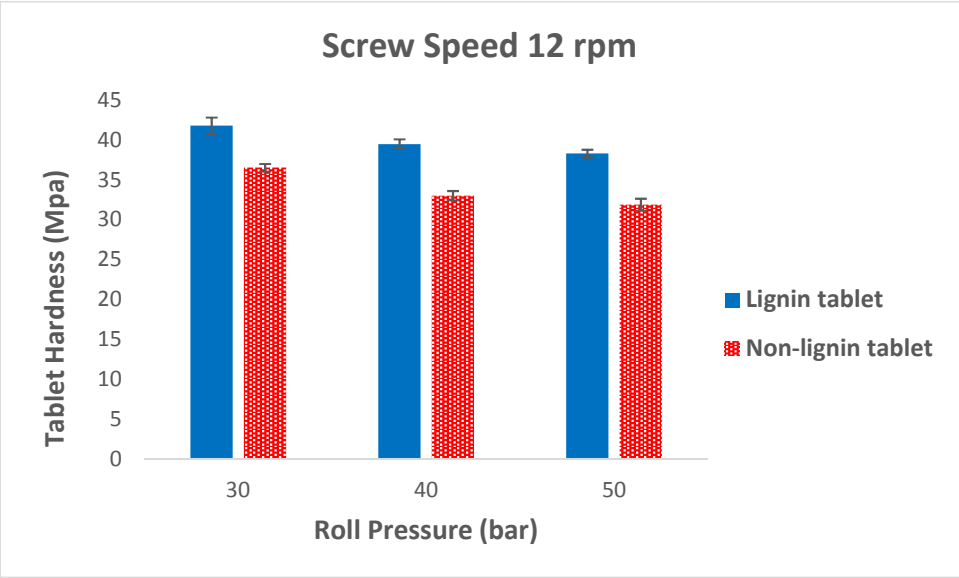


Figure S2: Variability of dissolution tests for formulations containing lignin and without lignin at different process parameters.


Roll Pressure 40 bar
Tablet Hardness (Mpa)
45
40
35
30
25
20
15
10
5
0
10
12
14
Screw Speed (rpm)
Non-lignin tablet
Lignin tablet


Screw Speed 10 rpm
Tablet Hardness (Mpa)
50
45
40
35
30
25
20
15
10
5
0
30
40
50
Roll Pressure (bar)
Lignin tablet
Non-lignin tablet



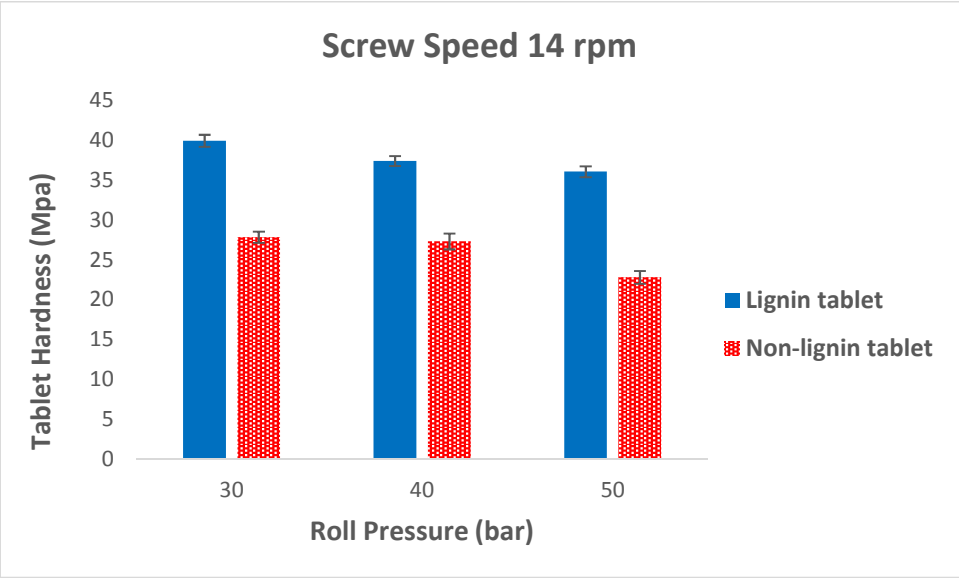
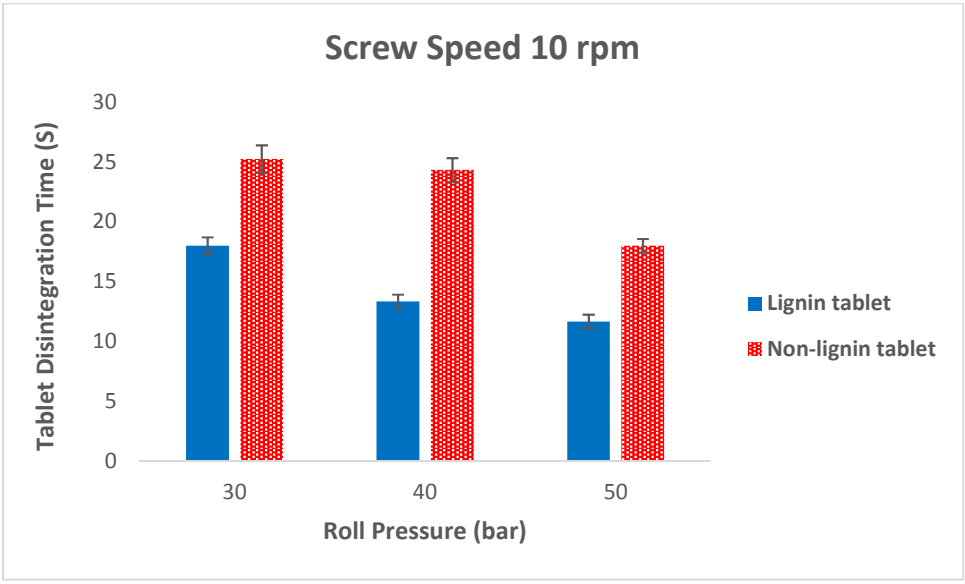
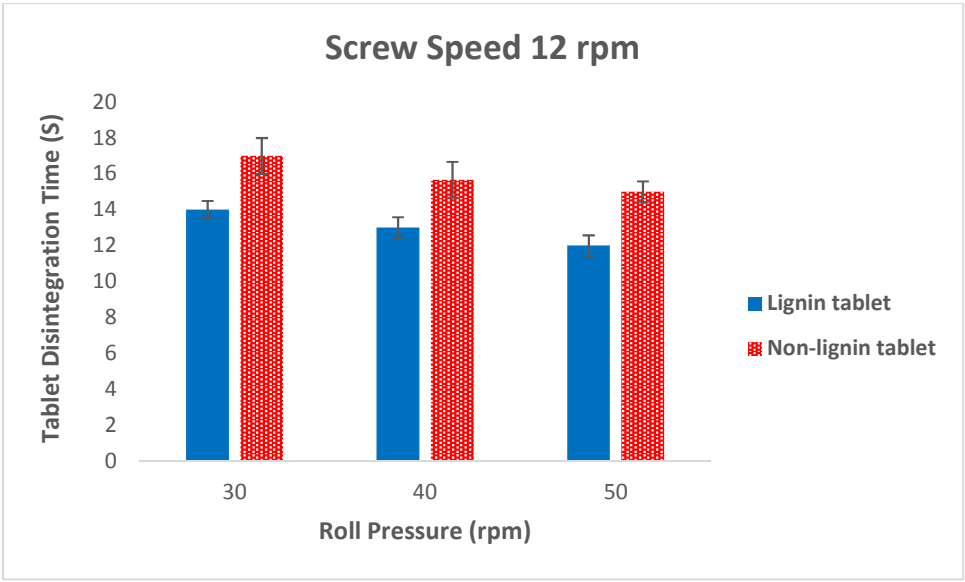


Figure S3. Error bars of tablet hardness for lignin tablet and non-lignin tablet at different process parameters


Screw Speed 10 rpm
Tablet Disintegration Time (S)
30
25
20
15
10
5
0
30
40
50
Roll Pressure (bar)
Lignin tablet
Non-lignin tablet


Screw Speed 12 rpm
Tablet Disintegration Time (S)
20
18
16
14
12
10
8
6
4
2
0
30
40
50
Roll Pressure (rpm)
Lignin tablet
Non-lignin tablet

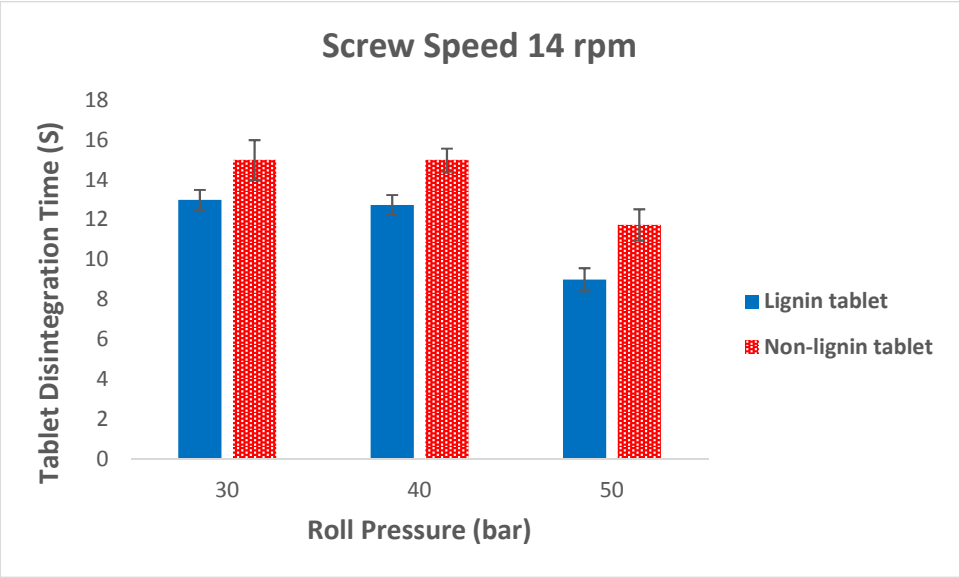


Figure S4. Error bars of tablet disintegration times for lignin tablet and non-lignin tablet at different process parameters

3. T-Test Analysis data

"An independent samples t- test was conducted to compare the means of "non-lignin tablet and lignin tablet" for 14 rpm screw speed. There was a significant difference between the mean of "1st variable", non-lignin tablet (mean=68.0034289, sd=5.07354) and "2nd variable", lignin tablet (mean=84.6754382, sd=7.27744) with t=-9.21 and $p < 0.001$".

"An independent samples t- test was conducted to compare the means of "non-lignin tablet and lignin tablet" for 12 rpm screw speed. There was a significant difference between the mean of "1st variable", non-lignin tablet (mean=71.71319637, sd=6.5463992) and "2nd variable", lignin tablet (mean=82.92867437, sd=8.588223) with t=-5.09 and $p < 0.001$".

Table 2. T-Test

t-Test: Two-Sample Assuming Equal Variances		
Non-lignin tablet/ Lignin tablet -14rpm screw speed	Variable 1	Variable 2
	Non-lignin tablet	*Lignin tablet*
Mean	68.0034289	84.6754382
Variance	25.7408246	52.9611617
Observations	24	24
Pooled Variance	39.3509932	
Hypothesized Mean Difference	0	
df	46	
t Stat	-9.20663055	
P(T<=t) one-tail	2.6356E-12	
t Critical one-tail	1.67866041	
P(T<=t) two-tail	5.2712E-12	
t Critical two-tail	2.0128956	

Table 3. T-Test

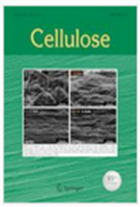
t-Test: Two-Sample Assuming Equal Variances		
Non-lignin tablet/ Lignin tablet -12 rpm screw speed	Variable 1	Variable 2
	Non-lignin tablet	*Lignin tablet*
Mean	71.71319637	82.92867437
Variance	42.85534259	73.7575801
Observations	24	24
Pooled Variance	58.30646134	
Hypothesized Mean Difference	0	
df	46	
t Stat	-5.088034748	
P(T<=t) one-tail	3.269E-06	
t Critical one-tail	1.678660414	
P(T<=t) two-tail	6.538E-06	
t Critical two-tail	2.012895599	

In chapter 2, the results are shown lignin is a good candidate to use as excipient in tablet formulation.

The results showed higher drug release rate for the formulation containing lignin, which was interesting. Then, we decided to model the drug release rate using Artificial Neural Network (ANN) and MATLAB to study the applicability of ANN modelling for drug release rate, which could be very useful to save time and materials.

Chapter 3.

Application of Lignin in controlled release: Development of predictive model based on artificial neural network for API release



Cellulose
July 2019, Volume 26, Issue 10, pp 6165–6178 | Cite as

Application of lignin in controlled release: development of predictive model based on artificial neural network for API release

Authors | Authors and affiliations

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Original Research
First Online: 25 May 2019

Application of Lignin in controlled release: Development of predictive model based on artificial neural network for API release

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Abstract

Predictive models for simulation of drug release from tablets containing lignin as excipient were developed in this work. Two predictive models including Artificial Neural Network (ANN) and hybrid ANN-Kriging were developed to simulate the tablet dissolution. Measured data was collected on the release rate of aspirin tablets prepared by dry granulation via roll compaction followed by milling and tableting. Two formulations were considered, one with lignin and one without. The main aim is to show the effect of lignin as a bio-based natural polymer in tablet manufacturing to control drug dissolution. For the ANN model development, process and formulation parameters including roll pressure and lignin content were considered as the input, while API dissolution was considered as response. The predictions were compared with measured data to calibrate and validate the model. To improve the predictability of the model, Kriging interpolation was used to enhance the number of training points for the ANN. The interpolated data was trained and validated. The final concentration and the dissolution rate were predicted by ANN as well as ANN-Kriging models, and the R^2 of greater than 0.99 for most cases was obtained. The validated model was used to evaluate the effect of process

parameters on the release rate and it was indicated that the tablets containing lignin have higher release rate compared to tablets without. Also, it was revealed that process parameters do not have significant effect on the tablet release rate, and the tablet release rate is mainly affected by the lignin content. The results indicated that ANN-based model is a powerful tool to predict the API release rate for tablets containing various formulations, and can be used as a predictive tool for design of controlled release systems.

Keywords: ANN model; Kriging interpolation; Controlled release; Lignin; Pharmaceuticals; Tableting; Dry granulation

1. Introduction

Most drugs are administered in solid phase, such as crystalline particles which are processed into tablets or capsules by adding excipients (Siepmann and Siepmann, 2013). In pharmaceutical manufacturing of solid-dosage oral formulations, there are different unit operations such as blending, granulation, drying, tableting, and coating among which granulation is the key processing step as the tablet properties depend on the granules attributes such as size, API content, porosity, etc. (Hansuld and Briens, 2014; Shirazian et al., 2018; Suresh et al., 2017; Vervaet and Remon, 2005). In granulation processes, pharmaceutical granules are formed from fine powder (e.g. excipient and API) using various methods such as roller compaction, high-shear wet granulation, twin-screw granulation, fluidised bed granulation, and hot melt extrusion (Asada et al., 2018; Hansuld and Briens, 2014; Ko et al., 2018; Passerini et al., 2010; Walker et al., 2007). The main reason for granulation is to improve the powder flowability as well as tablet properties. Among various granulation processes developed so far, dry granulation is a suitable process for moisture and heat sensitive formulations, as no binder is used in the process. Dry granulation is usually carried out using roller compaction process in which the formulation is first compacted to produce ribbons, and then granules are produced by milling the ribbons. The critical process parameters in roller compaction process include roll pressure, roll speed, roll gap, and screw feeder speed (Al-Asady et al., 2015; Omar et al., 2016).

Understanding the relationship between process parameters of the roll compaction process and tablet properties is of great importance for development of pharmaceutical manufacturing and implementing Quality-by-Design (QbD) approach. The effect of process parameters and material properties on critical quality attributes of ribbons and granules have been reported in literature. Both experimental (Khorasani et al., 2016; Khorasani et al., 2015) and theoretical studies (Loreti et al., 2017; Pérez Gago et al., 2016; Reynolds et al., 2010; Souihi et al., 2015) have been conducted to understand the roller compaction process. In terms of modelling studies, Johanson has proven to be a robust and rigorous mechanistic model for better understanding of roller compaction process (Reynolds et al., 2010). Although, previous studies reveal the correlation between critical process

parameters and granules/ribbons properties in roller compaction processes (Pishnamazi et al., 2018), understanding the relationship between process parameters and tablet dissolution still remains a challenge and opportunities arise in helping to improve tablet dissolution rate by tuning formulation and process parameters.

Drug dissolution is an important quality attribute of pharmaceutical tablets in which the kinetics and equilibrium concentration (solubility) of Active Pharmaceutical Ingredient (API) release from the tablets is of utmost importance (Siepmann and Siepmann, 2013). The main focus of controlled release systems is to manipulate the release rate of APIs through different techniques such as incorporating into polymeric matrix (Castro-Dominguez et al., 2017), and loading drug in stimuli-responsive nanocarriers (Fleige et al., 2012), and therefore enhancing bioavailability for poorly water soluble APIs. Nowadays, a big challenge facing the pharma industry is poor solubility of newly produced drugs in the body, i.e. bioavailability (Savjani et al., 2012). According to Biopharmaceutics Classification System, BCS Class II and BCS Class IV many drugs are of poor solubility and bioavailability (Daousani and Macheras, 2016). It has been recognised that seven out of ten of drugs never reach the patients. Development of solid dispersions have been reported to be effective in improving the solubility of BCS Class II drugs (Van den Mooter, 2012). Amorphous solid dispersions provide high dissolution rates because of their disordered structure and higher Gibbs free energy compared to crystalline APIs (Ziaee et al., 2017).

Recently, lignin has attracted much attention as it may be used to improve the release of bio-active compounds (Chowdhury, 2014; Collins et al., 2019). Lignin is a cross-linked natural polymer, cheap, and available (Culebras et al., 2018). Due to amorphous nature of lignin which has higher free energy, it can be used as modifier to enhance the bioavailability of poorly soluble APIs. However, understanding the effect of lignin on dry granulation using roller compactor, and finding a correlation between lignin content and tablet dissolution rate remains a big challenge. Developing a robust predictive model for designing controlled release systems based on natural polymers is of great importance for pharmaceutical industry.

Therefore, there is a definite need for a comprehensive study to correlate the critical process parameters of roller compactor as well as formulation with tablet dissolution as the key critical quality attribute. A powerful tool is the development of a process model where inputs and outputs can be correlated. Different models have been used for pharmaceutical manufacture such as mechanistic models (Sajjia et al., 2017; Shirazian et al., 2018) and soft computing approaches (Mustafa et al., 2017; Shirazian et al., 2017). Artificial Neural Network (ANN) is a soft computing method which is capable of predicting the process and making correlation between process inputs and outputs (Ismail et al., 2019a; Ismail et al., 2019b). Applicability, robustness, and reliability of ANN in pharmaceuticals have been verified in the literature (Das and Chakraborty, 2016; Mustafa et al., 2017; Shirazian et al., 2017).

The main objective of the current study is the development of a comprehensive ANN-based model for prediction of dissolution rate of tablets prepared by roller compaction followed by milling and tableting. In order to enhance the bioavailability of API, lignin is used as excipient and the tablet dissolution rate is measured for tablets containing lignin and without lignin. Aspirin is used as model API in this study.

2. Experiments

2.1. Materials and Methods

Two formulations containing API and excipients were considered in this study for preparation of tablets. The excipients used include microcrystalline cellulose (MCC 102, SANAQ®), lactose monohydrate (Lennox USP, NF, BP, Ph, pure pharma grade), and Alcell lignin (Tecnaro, Germany). More details on the lignin used in this study can be found elsewhere (Culebras et al., 2018). Acetylsalicylic acid (Alfa Aesar, 99% $C_9H_8O_4$) was utilised as API in both formulations. Magnesium stearate (Sigma-Aldrich, Ph. Eur., BP, ≥90%) was used as lubricant for the compaction experiments, and Croscarmellose sodium (CCS) (IMCD NF, PH.Eur., JP) was used as disintegrant in both formulations. The percentage of the materials used in two different formulations are listed in Table 1. To prepare the mixture, all the materials were blended using a Morphy Richards Stand Mixer. HCl

acid (ACS, ISO, Reag. Ph Eur, Hydrochloric acid fuming 37%) was used for preparation of buffer solutions for dissolution tests. For preparation of the mobile phase for analysing the API concentration with HPLC, Ortho-phosphoric acid (analytical reagent grade, Fisher Scientific UK) and acetonitrile, HPLC grade, 99.7+% min Liquid (Alfa Aesar) were mixed together.

Table 1. Different formulations used in this work.

Material (% w/w)	Formulation 1	Formulation 2
Acetylsalicylic acid	5	5
Alcell lignin	20	0
Lactose	20	20
MCC 102	51	71
Croscarmellose sodium	3	3
Magnesium stearate	1	1

2.2. Equipment and instruments

Dry granulation method was utilised to produce the tablets for two different formulations. In order to do dry granulation process, roller compaction was carried out. The roller compactor, Freund TF-MINI (Vector Corporation, Japan) with roll diameter of 100 mm and width of 25 mm integrated with a vertical screw feeder was used to produce ribbons. The roll pressure was changed between 30 and 50 bar in the experiments. A conical mill (Laboratory Comil 193 AS, Quadro, USA) with a screen (mesh size of 813 µm) and impeller speed of 3000 rpm was used to produce the granules from the ribbons. The considered process parameters included screw speed (SS) and roll pressure (RP), while roll speed was kept constant at 4 rpm. The screw speed was changed between 10-14 rpm, and roll pressure was changed between 30-50 bars in the ribbon production experiments.

For tableting process, a single punch tablet press (Gamlen Tableting GTD-1 D series, UK) was applied. For preparation of each tablet, 100 mg of granules of each formulations were measured and compacted to produce tablets in a 6 mm die. The tablet compression was carried out at 180 mm/min speed under fixed load of 400 kg.

2.3. Dissolution procedure

For the dissolution analysis, buffer solution at pH= 1.2, including 0.1 N HCl (ACS, ISO, Reag. Ph Eur, Hydrochloric acid fuming 37% wt.) was prepared as dissolution medium. 500 ml of the dissolution test chamber was filled with the buffer solution, with the constant temperature at 37 ± 0.5 ˚ C and 75 rpm stirrer speed. The experiment was run for 120 minutes, and the samples (Three mL) were withdrawn from the dissolution chamber at 5, 10, 20, 30, 40, 50, 60, 120 minutes. Afterward, the samples were filtered and the concentration of API was measured using HPLC at wavelength of 200 nm. The dissolution tests were carried out in triplicate, and the average values were used for modeling.

High-Performance Liquid Chromatography (HPLC) was used to measure the API concentration in each samples via an Agilent (Agilent Technologies, Waldbronn, Germany) 1260 Infinity II HPLC system. The HPLC setup consisted of a quaternary pump G1311B, a diode array detector G1315D set at wavelengths of 200 nm for acetylsalicylic acid, auto-sampler G1329 B and a thermostated column compartment G1316A set at temperature of 25 ˚C. The system operated under isocratic flow at 0.75 mL/min using mobile phases consisting of A) 0.1 % Ortho-phosphoric acid; B) acetonitrile; A/B =50/50, v/v. The injection volume was 10 mL. The total run time was 10 minutes, and the type of column used was Kromasil 5C18 (250×4.6 mm) (Pishnamazi et al., 2019).

3. Model development

3.1. ANN structure

In order to develop a predictive model, artificial neural network (ANN) approach was used in which the process parameters and material properties are correlated with critical quality attributes. Roll pressure, screw speed, and lignin content in the formulation were considered as the inputs, whereas the kinetics and final API dissolution were considered as outputs for developing ANN. The preliminary results indicated that screw speed has negligible effects on the quality attributes of ribbons, therefore, screw speed was omitted from the process parameters. An ANN model consisting

of two hidden layers was developed as shown in Fig. 1. *JMP Pro 14* software was used for developing the ANN model and analysing the results.

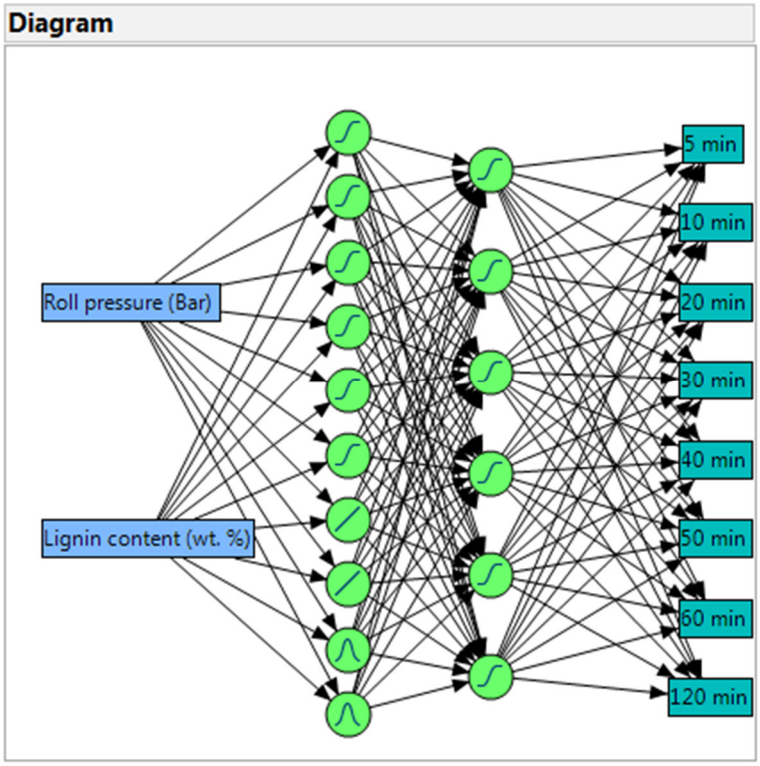


Figure 1. Structure of developed ANN for prediction of drug release.

To find the optimum ANN structure, different transfer functions were tested, and the best results were obtained for the structure consisting of 6 non-liner (hyperbolic tangent), 2 liners, and 2 Gaussian functions in the first layer; with 6 non-linear nodes for the second layer (see Fig. 1). In ANN modelling using *JMP*, the linear combination of input variables (roll pressure and lignin content) are not transformed when using the linear activation function, while for the non-linear function, the hyperbolic tangent term is used as follows (SAS_Institute, 2016; Shirazian et al., 2017):

$$\frac{e^{2z}-1}{e^{2z}+1} \qquad (1)$$

where z is a linear combination of input variables.

In order to build ANN model, 60 % of the measured data was used to train the network, while 40% was used for model validation and testing the developed model in prediction of the API release rate.

The network was trained to predict the concentration of API at different sampling time intervals, as function of lignin content and roll pressure of roller compactor. The developed ANN model was used for prediction of API release rate, in which the predictive behaviour and accuracy of the model is assessed by comparing the predicted values and the measured values. The coefficient of determination (R^2) which indicates the goodness of fitting is calculated as (Barrasso et al., 2015; Shirazian et al., 2017):

$$R^2 = 1 - \frac{\sum_i (f_i - y_i)^2}{\sum_i (\bar{y}_i - y_i)^2} \tag{2}$$

where f refers to the predicted points, and y refers to the observed values. i denotes the set of experimental run. Also, root-mean-squared error (*RMSE*) is calculated as:

$$\mathrm{RMSE} = \sqrt{\frac{\sum_i (f_i - y_i)^2}{n}} \tag{3}$$

where n denotes the number of measurements.

3.2. ANN-Kriging hybrid model

In order to improve the predictability of the developed ANN model for API dissolution, Kriging interpolation method was used to enhance the number of training and validating points for the ANN. Ordinary Kriging interpolation was developed based on two inputs and eight outputs which are the dissolution percentage at various times. Kriging method predicts a response y_k at an interpolated point x_k as a weighted sum of the observed responses (y_1,y_2…y_n) where x_k falls in the neighbourhood of their corresponding sampling points (x_1,x_2,x_3…x_n) (Boukouvala et al., 2011):

$$y_k = f(x_k) = \sum_{i=1}^{n} w_i f(x_i) \tag{4}$$

w_i is the weighted sum (kriging weights) which depends on the Euclidian distance h:

$$h = \|x_i - x_j\| \tag{5}$$

In Kriging algorithm, the main objective is to calculate the set of Kriging weights assigned to each group of *n* clustered points in the neighbourhood of x_k where the derived variogram model leads the sum of the weights to unity. In calculating the interpolated prediction $f(x_k)$ at x_k, the observed responses (y_1,y_2…y_n) for sampled points (x_1,x_2,x_3…x_n) that are in the neighbourhood and nearer to x_k will have more influence on predicting $f(x_k)$. Indeed, the higher number of neighbouring points and the nearer these neighbouring points are to x_k, $f(x_k)$ will be calculated with more confidence (Ismail et al., 2019a; Ismail et al., 2019b).

In ordinary kriging interpolation, the experimental variogram is calculated from the experimental data points to statistically quantify the dataset in a form that fits statistical equations (exponential, Gaussian, cubic…etc.). After fitting the experimental and theoretical variograms, kriging weights are then calculated to determine the interpolated response.

A two-dimensional kriging interpolation was conducted on the experimental data obtained from the dissolution experiments to predict the dissolution of API at new data points. The reliability and validity of the hybrid ANN-kriging has been proved in our previous works (Ismail et al., 2019a; Ismail et al., 2019b). Ordinary Kriging interpolation was performed in *Matlab* where the lignin content (%) and roller pressure (bar) were taken as input parameters and API dissolution at 5, 10, 20, 30, 40, 50, 60 and 120 minutes as output parameters. Interpolation was conducted at 10 new points for each dimension in which 121 points were obtained after applying Kriging. The interpolated kriging data was used to improve the empirical ANN model prediction compared to using just experimental data.

The structure of the developed ANN-Kriging is shown in Fig. 2. As seen, the hybrid model contains two hidden layers, each layer constitutes of three nodes which makes the model simpler and faster to solve. Also, a combination of linear and nonlinear transfer functions has been used for the hybrid model to train the network for prediction of data.

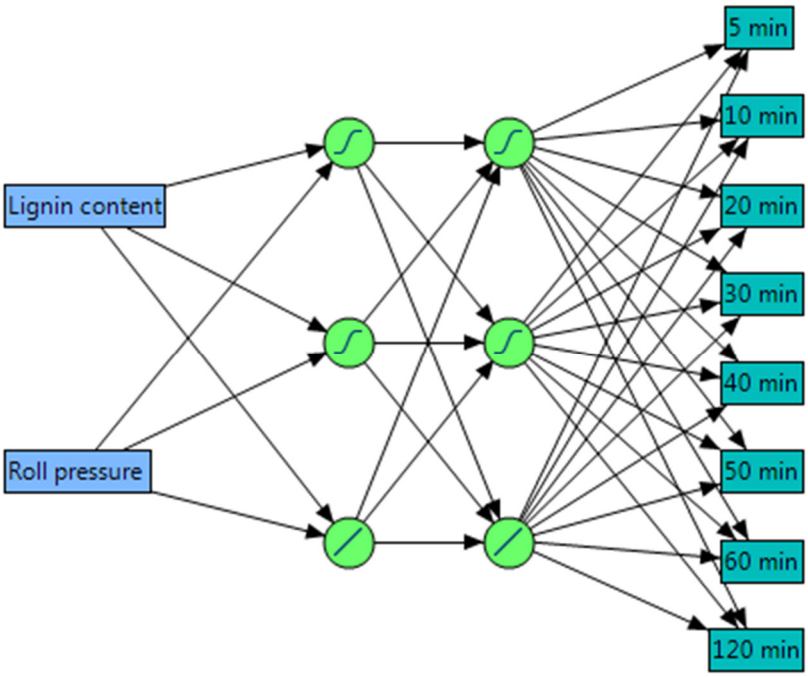


Figure 2. Structure of developed ANN-Kriging hybrid model for prediction of drug release.

4. Results and discussion

4.1. ANN model

The developed ANN model was first trained using the experimental data collected on the release rate of tablets containing aspirin. The trained network was then used to validate the model. The results of training and validation are listed in Table 2 for the concentration of API at different times, and the final concentration of API at the time of 120 minutes (final). As seen, the model is very well trained with the experimental data, and the R^2 of 1 is obtained for all points, while for the validation R^2 of 0.99 is obtained for most cases except for predicting the concentration of API after 5 minutes which could be attributed to high release rate at the beginning of the dissolution test. It is clearly observed that the model can predict the release rate of API with high accuracy, and can be used as a powerful predictive tool for the design of release systems based on lignin. However, it should be pointed out that there might be a risk of over-prediction in this system as small number of experimental points

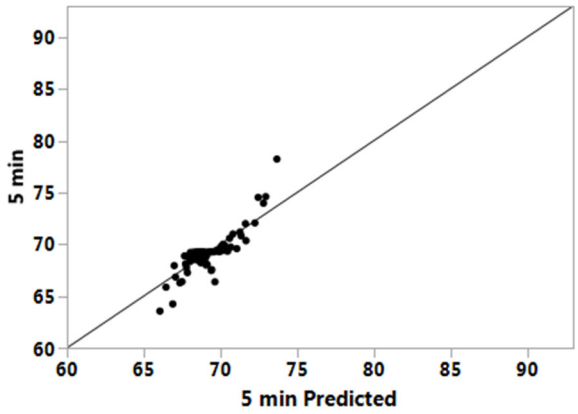
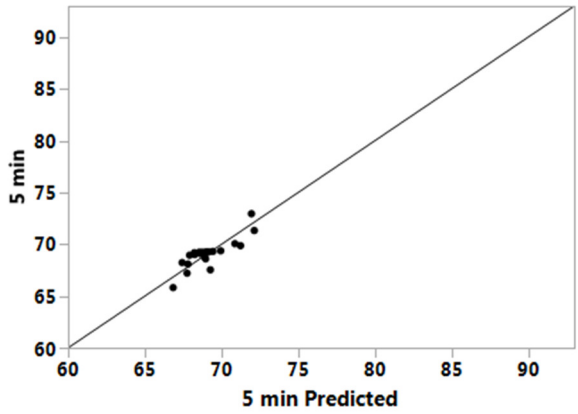
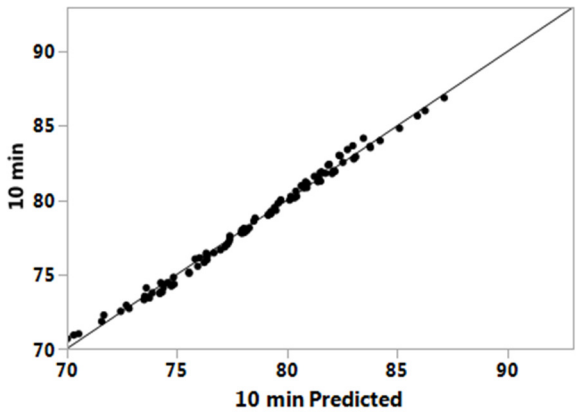
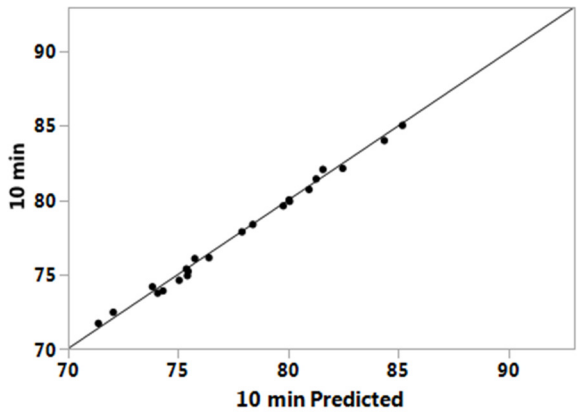
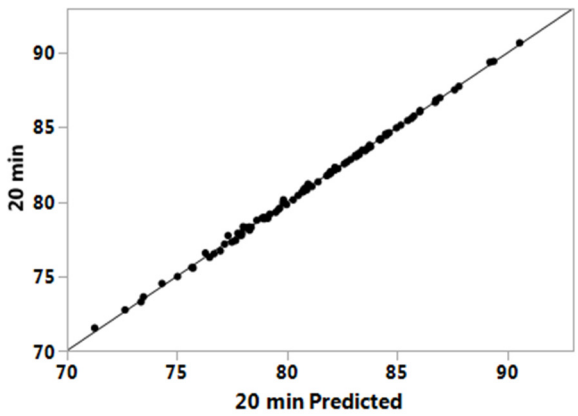
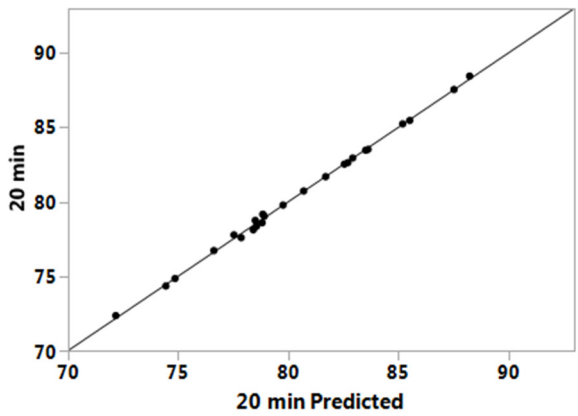
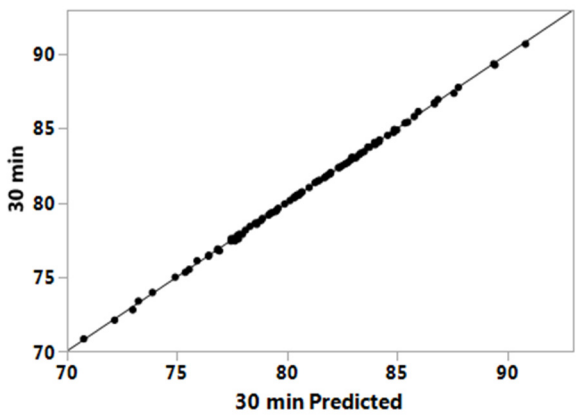
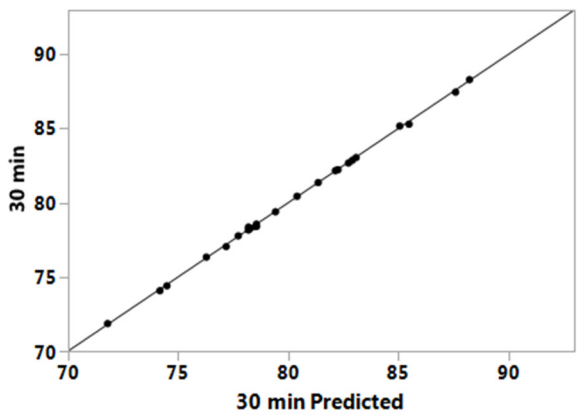
are used. Therefore, Kriging approach was used to train the network for more data points and prevent the risk of over-prediction.

Table 2. Statistical data of ANN calibration and validation.

times	Data set	R^2	RMSE	Mean Abs Dev	-Log Likelihood	SSE	Data points
5 min	Training	1	8.7e-13	7.5e-13	-105.4	3.0e-24	4
	Validation	0.52	2.6	1.9	4.8	14.0	2
10 min	Training	1	2.1e-13	1.8e-13	-110.9	1.9e-25	4
	Validation	0.99	0.2	0.2	-0.2	0.1	2
20 min	Training	1	3.7e-13	3.2e-13	-108.8	5.6e-25	4
	Validation	0.99	0.5	0.4	1.5	0.5	2
30 min	Training	1	4.3e-13	3.7e-13	-108.2	7.3e-25	4
	Validation	0.99	0.6	0.6	1.7	0.6	2
40 min	Training	1	4.3e-13	3.7e-13	-108.2	7.5e-25	4
	Validation	0.99	0.4	0.4	1.1	0.4	2
50 min	Training	1	2.9e-13	2.4e-13	-109.8	3.3e-25	4
	Validation	0.91	1.5	1.4	3.7	4.7	2
60 min	Training	1	4.1e-13	3.5e-13	-108.4	6.7e-25	4
	Validation	0.99	0.1	0.1	-0.9	0.04	2
120 min	Training	1	4.0e-13	3.3e-13	-108.5	6.4e-25	4
	Validation	0.99	0.3	0.3	0.6	0.2	2

4.2. ANN-Kriging model

The predicted release rate versus the measured values for both training and validation for the hybrid ANN-Kriging model are depicted in Fig. 3. Moreover, the statistical data of the calibration and validation for the hybrid ANN-Kriging is listed in Table 3. After Kriging, the number of data points are increased to 121 points to make a more robust predictive model. 1/3 of the data points were used for validation, while 2/3 were used for training the network. It is clearly seen that the model is well trained for all the training points and the cross validation can confirm the model can be used for prediction of the dissolution. Also, similar to the ANN model, some deviations are observed for the dissolution data after 5 minutes, however R^2 has been significantly improved for 5 minutes data from 0.52 to 0.67 for the validation stage.

Training	Validation	
		A: 5 mins
		B: 10 mins
		C: 20 mins
		D: 30 mins

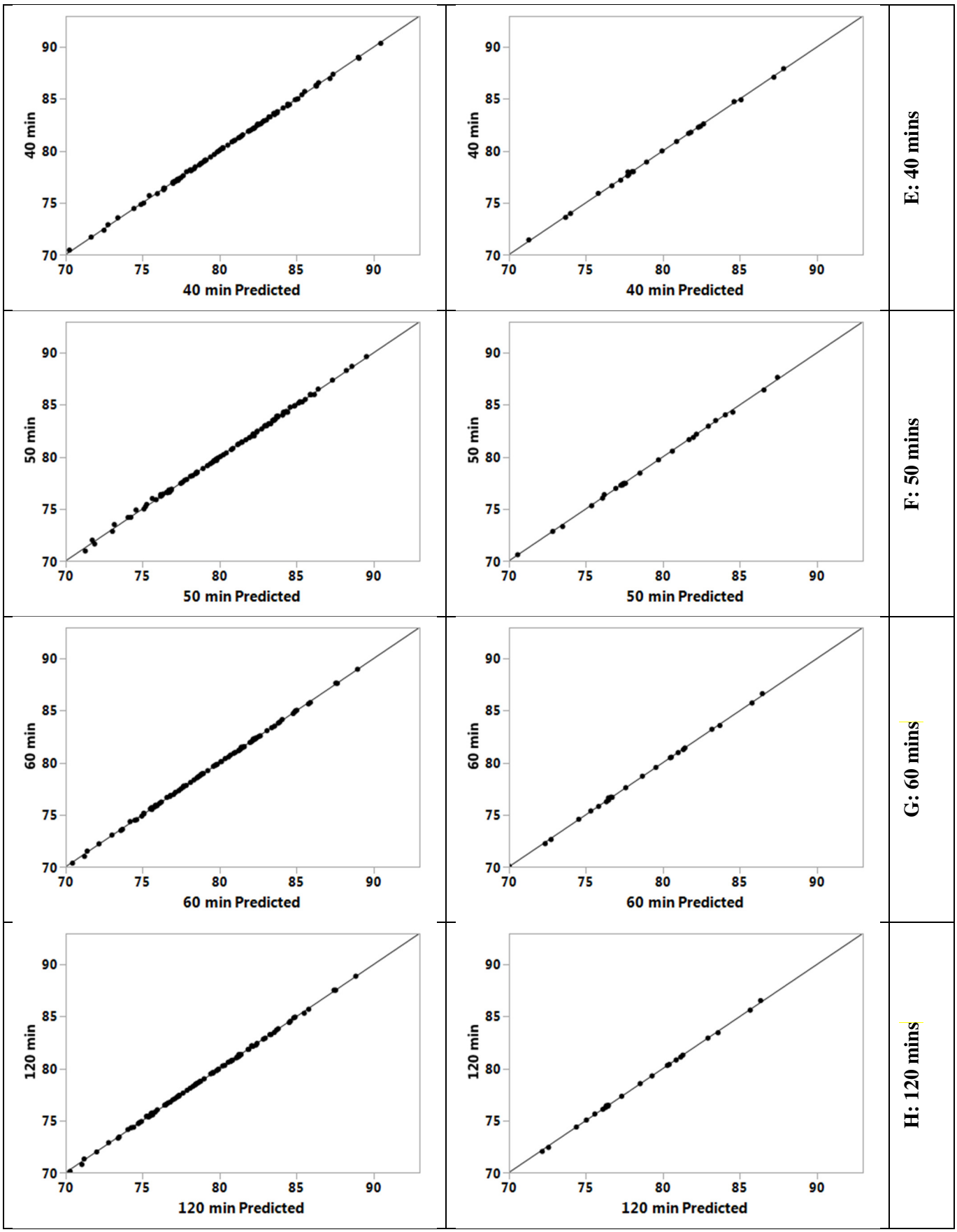


Figure 3. Actual versus predicted values of drug release for the hybrid ANN-Kriging model. A: 5 mins, B: 10 mins, C: 20 mins, D: 30 mins, E: 40 mins, F: 50 mins, G: 60 mins, H: 120 mins.

Table 3: Statistical data of hybrid ANN-Kriging calibration and validation.

times	Data set	R^2	RMSE	Mean Abs Dev	-Log Likelihood	SSE	Data points
5 min	Training	0.69	0.98	0.68	135.83	93.45	97
	Validation	0.67	0.89	0.71	31.15	18.84	24
10 min	Training	0.99	0.34	0.27	32.50	11.10	97
	Validation	0.99	0.30	0.26	5.54	2.23	24
20 min	Training	0.99	0.13	0.09	-60.92	1.62	97
	Validation	0.99	0.14	0.10	-12.88	0.48	24
30 min	Training	0.99	0.07	0.05	-113.76	0.54	97
	Validation	0.99	0.07	0.06	-27.58	0.14	24
40 min	Training	0.99	0.07	0.057	-116.05	0.52	97
	Validation	0.99	0.07	0.05	-27.56	0.14	24
50 min	Training	0.99	0.10	0.07	-83.30	1.02	97
	Validation	0.99	0.12	0.08	-16.13	0.36	24
60 min	Training	0.99	0.06	0.05	-133.06	0.36	97
	Validation	0.99	0.06	0.05	-31.47	0.10	24
120 min	Training	0.99	0.07	0.05	-120.85	0.47	97
	Validation	0.99	0.07	0.05	-29.28	0.12	24

4.3. Simulation of the release rate using ANN model

The validated model was used to simulate the release rate of API for the tablets prepared with two formulations. The experimental and predicted release rates for the tablet without lignin, and the tablets containing lignin are represented in Figs. 4 and 5, respectively. The graphs of release rate indicate that the release rate is very high at the beginning of dissolution test, and more than 60 % of the API is released after 5 minutes. After 20 minutes, the drug concentration in the solution reaches the highest values, and then decreases, and finally become plateau which is considered as the equilibrium point. The reason for reduction in the concentration of API after 20 minutes could be attributed to the dissociation of aspirin which undergoes hydrolysis during the dissolution test. Aspirin is partially hydrolysed to salicylic acid and acetyl salicylic acid upon exposure to aqueous solutions (Pishnamazi et al., 2019).

It is also observed in Figs. 4 and 5 that the release rate of aspirin is higher in the tablets containing lignin such that higher dissolution rate is observed in the dissolution test of tablets containing lignin. This could be due to amorphous nature of lignin which enhances the dissolution of aspirin. It is observed that the model is robust and can predict the release rate and the final concentration as well.

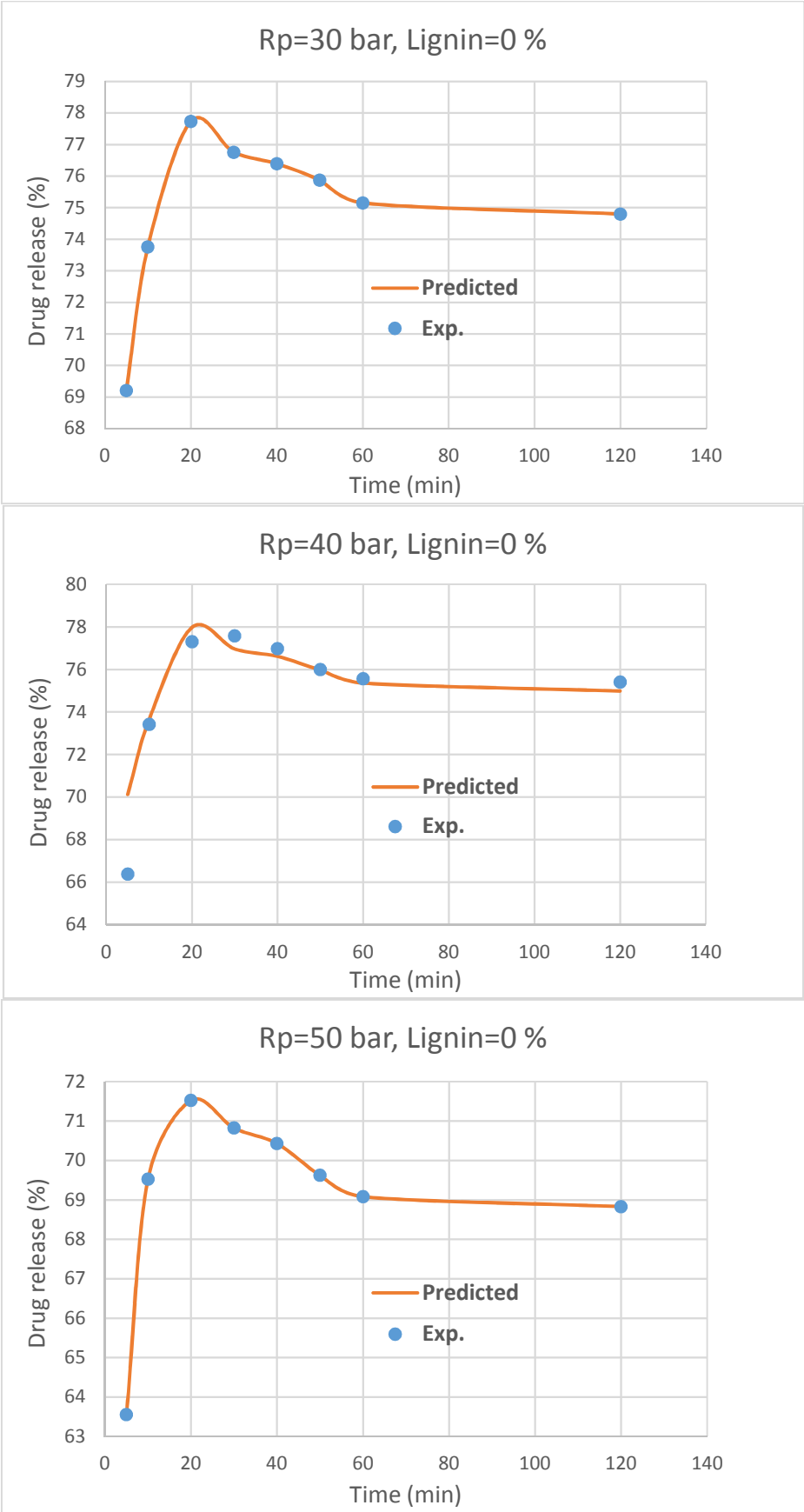


Figure 4. Comparison between simulated and measured values of drug release. Tablets with no lignin. ANN model.

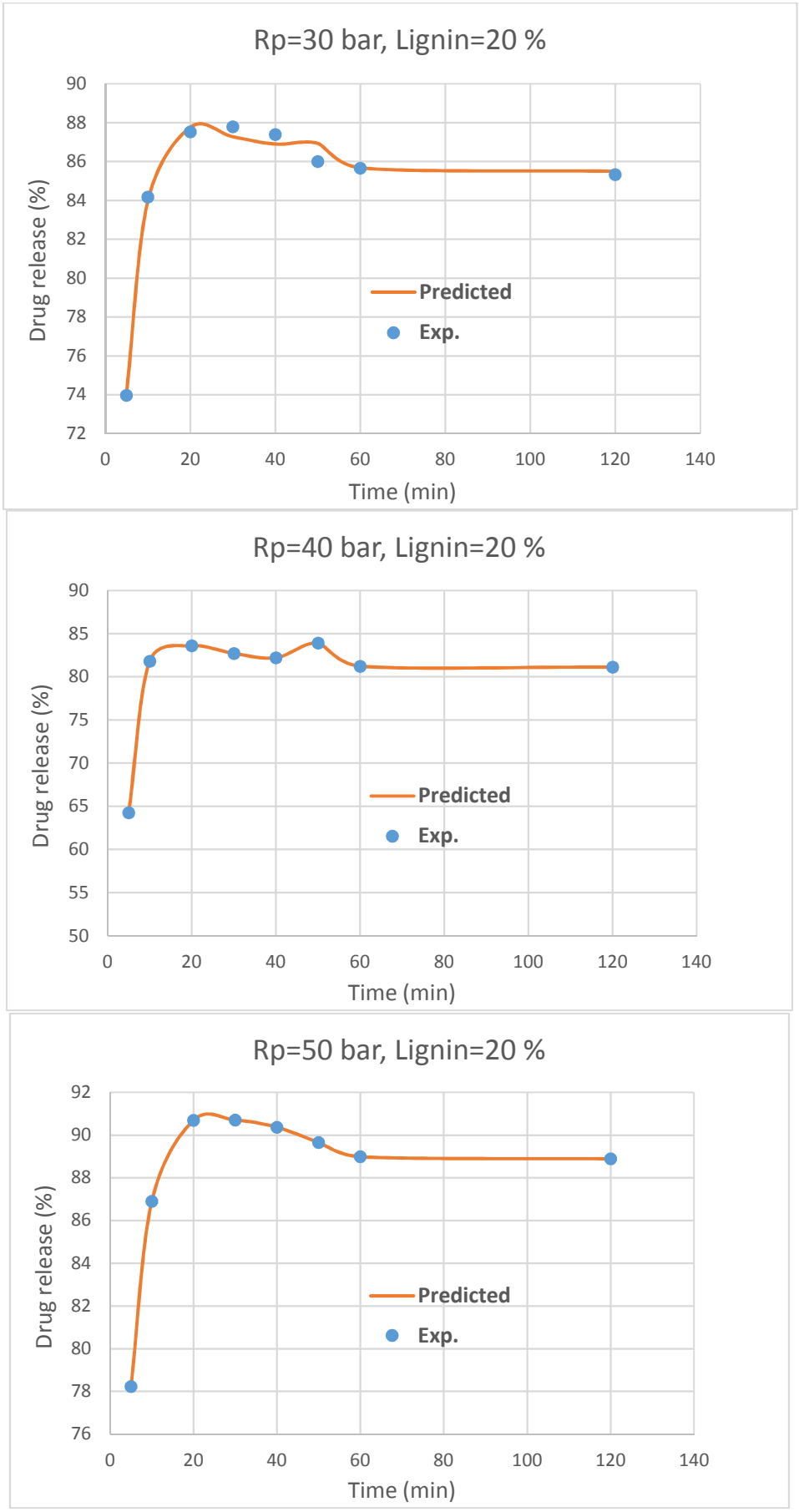
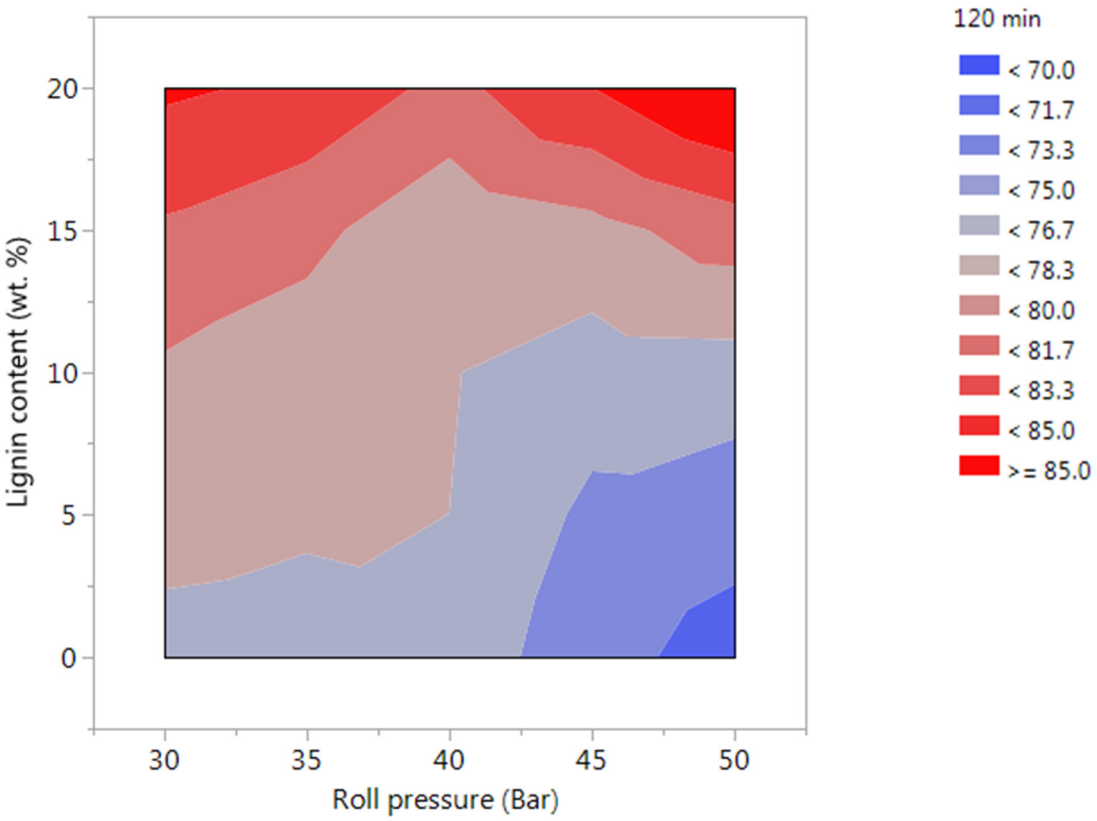


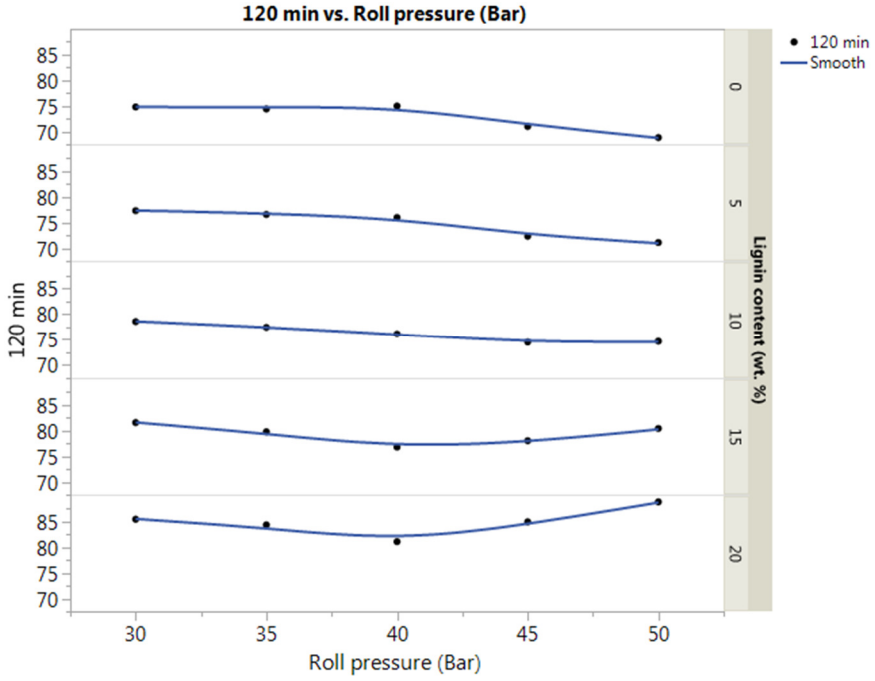
Figure 5. Comparison between simulated and measured values of drug release. Tablets with lignin. ANN model.

4.4. Design space for the API release

The developed model was used to understand the effect of process parameters of roll compaction as well as formulation on the release rate of API. In roller compaction process, roll pressure is the most important parameter compared to other parameters such as screw speed and roll speed (Pishnamazi et al., 2018). The effect of roll pressure and lignin content on the equilibrium concentration of API in the buffer solution is shown in Fig. 6. The roll pressure was considered between 30-50 bar, and the lignin content between 0-20 wt. %. It is indicated that by increasing the lignin content in the formulation, the dissolution of API increases significantly which consequently can enhance the bioavailability of API. Also, it is seen that by increasing the pressure, the dissolution decreases, however the effect of roll pressure on the dissolution is not significant compared to the effect of lignin content because the dissolution of API is highly dependent on the chemistry of formulation and the dissolution medium. It is observed that increasing roll pressure decreases the equilibrium concentration of API which is attributed to the size of granules. As the roll pressure increases, denser ribbons are produced, which results in formation of larger granules in the milling step. Larger granules in the prepared tablets results in lower dissolution as the surface area of the granules decreases and reduce the surface energy and dissolution.



(a)



(b)

Figure 6. Prediction profiler; (a) Contours of equilibrium drug release versus roll pressure and lignin content; (b) graph builder.

5. Conclusions

A new formulation containing lignin was designed in this work to enhance the bioavailability of drugs. The tablets were prepared using dry granulation method followed by milling and tableting. In order to design and predict the release rate of API, an artificial neural network (ANN) model was developed considering two hidden layers and combining various activation functions, i.e. linear, hyperbolic tangent, and Gaussian. The ANN model as well as hybrid ANN-Kriging were developed to predict the dissolution of the drug. Two formulations, one containing lignin, and the other one without lignin were considered to investigate the effect of lignin on the API release rate. The results of release rate indicated that the tablets containing lignin have higher release rates of API. The results of simulation revealed that the developed model can predict the release rate with high accuracy and R^2=0.99 was obtained for most cases. The model was used to predict the kinetics and equilibrium of the release rate and great agreement was obtained between the predicted and measured data. The validated model was then used to understand the effect of process parameters on the release rate, and it was revealed that increasing roll pressure decreases the release rate, because larger granules are produced which in turn results in lower release rate.

Acknowledgements

This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750.

The authors declare no conflict of interest.

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Appendix

MATLAB codes for ANN-Kriging

```
syms H1 H2 H3 HH1 HH2 HH3 THETA1 THETA2 THETA3 THETA4 THETA5 THETA6 THETA7 THETA8 Lignin_content Roll_pressure P_5minP P_10minP P_20minP P_30minP P_40minP P_50minP P_60minP P_120minP

H1 = tanh(.5*(-0.00066184740102217*Lignin_content + -0.262662295436883*Roll_pressure + 10.7736115523835));

H2 = tanh(.5*(-0.136798865827418*Lignin_content + -0.0040891931727841*Roll_pressure + 3.3928495955642));

H3 = -0.00218360187333637*Lignin_content + -0.0534606845680695*Roll_pressure + 1.59699424536851;

HH1 = tanh(.5*(0.0573689661011285*H1 + 0.133071274895432*H2 + 4.66486177669116*H3 + 2.73303458525506));

HH2 = tanh(.5*(-0.646613009218206*H1 + 3.53607870921569*H2 + 0.298338609051791*H3 + -5.69556454905895));

HH3 = -3.09553015309569*H1 + -0.223555991654973*H2 + -0.0119944460569438*H3 + 0.305811189255288;

THETA1=82.9337628695886*HH1 + -40.4828651722123*HH2 + 26.6942842353261*HH3 + 28.6416291130038;

THETA2=45.256568606753*HH1 + -102.460433397237*HH2 + 15.2914341147021*HH3 + -18.4248999808702;
```

```
THETA3=70.4357629968306*HH1 + -106.389397832412*HH2 + 23.1996064208961*HH3 + -19.9013009015741;

THETA4=84.9814457018386*HH1 + -110.249292252343*HH2 + 27.8655615136839*HH3 + -24.3081298033377;

THETA5=86.129712919647*HH1 + -111.103076883315*HH2 + 28.2422914255355*HH3 + -25.5981943315789;

THETA6=51.8758851431266*HH1 + -109.255967707215*HH2 + 17.3619957166247*HH3 + -22.9409067484738;

THETA7=78.7848318048491*HH1 + -109.616704184623*HH2 + 25.9123561080872*HH3 + -25.2741546049034;

THETA8=77.7836793586035*HH1 + -109.89119137311*HH2 + 25.6239094541334*HH3 + -25.6906303502175;

P_5minP = THETA1;

P_10minP = THETA2;

P_20minP = THETA3;

P_30minP = THETA4;

P_40minP = THETA5;

P_50minP = THETA6;

P_60minP = THETA7;

P_120minP = THETA8;

digetsOld = digits(4);

P_5minP = vpa(P_5minP);
```

```
P_10minP = vpa(P_10minP);

P_20minP = vpa(P_20minP);

P_30minP = vpa(P_30minP);

P_40minP = vpa(P_40minP);

P_50minP = vpa(P_50minP);

P_60minP = vpa(P_60minP);

P_120minP = vpa(P_120minP);
```

In the previous three chapters, we studied the lignin characterization, in terms of powder and granules. Then we used lignin as excipient to study the effect of that on drug release behaviour. Moreover, we modelled the drug release rate using ANN software. All the results were satisfactory. Then, for the next step, we decided to modify lignin, as it is a good candidate for chemical modification due to different fictional groups on the lignin structure, which is very useful to enhance drug release rate. We decided to study the effect of modified lignin on drug release rate and we used another type of API, to make sure lignin can be used as excipient in the tablet formulation with different types of API. Then, we decided to study controlled-release behaviour of lignin as key parameters in drug release.

Chapter 4.

Design of controlled release system for paracetamol based on modified lignin

polymers

MDPI

Article

Design of Controlled Release System for Paracetamol Based on Modified Lignin

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Received: 15 April 2019; Accepted: 15 June 2019; Published: 18 June 2019

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Design of controlled release system for paracetamol based on modified lignin

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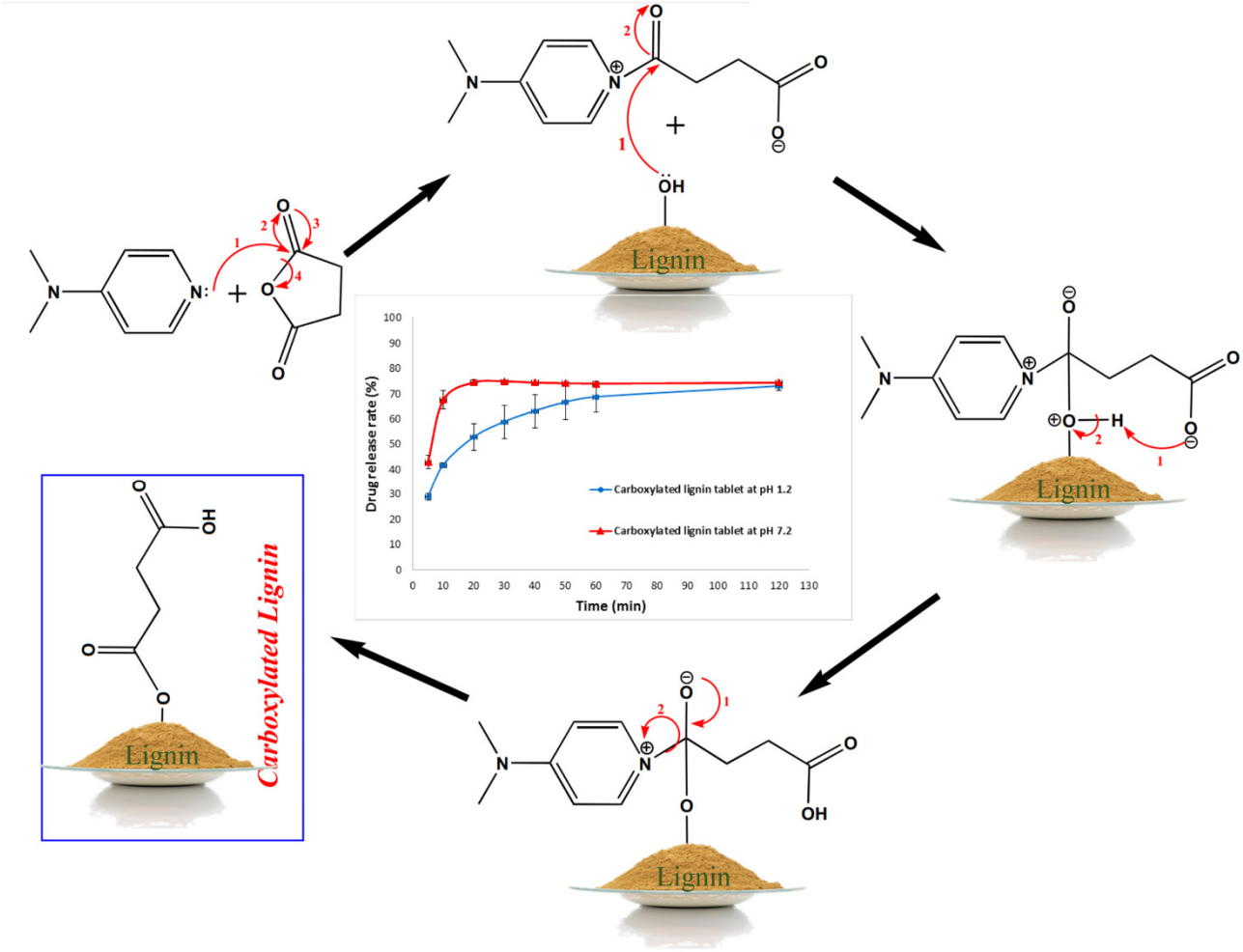
Abstract

The influence of lignin modification on drug release and pH-dependent releasing behaviour of oral solid dosage form was investigated using three different formulations. The first formulation contains microcrystalline cellulose (MCC101) as excipient and paracetamol as active pharmaceutical ingredient (API). The second formulation includes Alcell lignin and MCC 101 as excipient and paracetamol, and the third formulation consists of carboxylated Alcell lignin, MCC 101 and paracetamol. Direct compaction was carried out in order to prepare the tablets. Lignin can be readily chemically modified due to the existence of different functional groups in its structure. The focus of this investigation is on lignin carboxylation and its influence on paracetamol control release behaviour at varying pH. Results suggest that carboxylated lignin tablets had the highest drug release, which is linked to their faster disintegration and lower tablet hardness.

Keywords: Lignin; Drug Release; Paracetamol; Disintegration;

Graphical Abstract



1. Introduction

Excipients play a significant role in the final product of pharmaceutical solid dosage forms. Variations in excipient properties influence tablet processability, hardness, disintegration and bioavailability [1-3]. Nowadays, many researchers have focused their investigations on using natural biopolymers [4] in tablet manufacturing due to their biocompatibility [5,6], also, they are cheap and widely available [7-9]. Lignin is a natural biopolymer with a number of beneficial properties including biodegradability and biocompatibility [10-14]. Recently, the use of lignin is increasing as a sustainable polymer for preparing carbon fibers [15], biofuels, bioplastics and controlled release carriers [16-21]. Due to the existence of different functional groups in the lignin structure such as; phenolic, hydroxyl and carboxyl groups, lignin can be chemically modified to enhance drug delivery and to control drug release [22-24]. Figueiredo et al. functionalized Kraft lignin nanoparticles by carboxylation in order to improve drug delivery of poorly water-soluble anti-cancer drugs which were pH-sensitive [18]. Lievonen et al. modified softwood Kraft lignin using a dialysis technique to improve its drug delivery performance [25]. Furthermore, it has been recognized that pH-responsive drug carriers provide superior drug delivery characteristics due to their ability to increase stability of API (active pharmaceutical ingredient) molecules in the stomach and release API in the intestine [26]. Li et al. investigated the release behavior of ibuprofen, using lignin-based complex micelles. The results of release tests illustrated a pH-dependent and controlled release properties due to ionization of the carboxyl groups in the lignin structure, with repulsive forces between the negatively-charged carboxyl groups of lignin and API molecules, with higher solubility of API at pH=7.4 [27]. Chen et al. synthesized lignin-based pH-responsive nano-capsules to improve controlled release of poorly water-soluble drugs by varying pH [28]. Duval et al. studied pH and light responsive behavior of controlled-release systems containing diazobenzen and modified softwood Kraft lignin [29]. Various investigation have been carried out on the effect of lignin-based polymeric nanoparticles (NPs) on the controlled release of pesticides [30,31].

Bulut et al. studied the controlled-release behavior of paracetamol using chitosan-graft-polyacrylamide microspheres via an emulsion crosslinking technique [32]. They utilized glutaraldehyde (GA) as crosslinker to investigate the effect of that on the drug release rate. They mentioned the drug release rate was affected by some parameters such as the amount of GA, copolymer concentration and drug and polymer's composition. Their results illustrated more controlled release of drug by increasing the GA amount and copolymer, and decreasing in composition (paracetamol/polymer) ratio. Treenate et al. investigated the controlled release properties of paracetamol using a novel system composed of hydroxyethylacryl chitosan and sodium alginate in order to improve drug delivery for oral dosage forms [33]. Through improving drug water solubility, drug efficiency will be improved [34]. The current authors have evaluated the effect of lignin on the release rate of aspirin in oral dosage form, and indicated the higher release rate of drug using lignin as excipient in the tablet formulation [9].

In this study, the effect of carboxylated lignin as excipient on paracetamol release behavior was investigated. Lignin carboxylation was performed to enhance the carboxyl group content on the lignin surface in order to increase the interactions between lignin and paracetamol functional groups and allow pH triggered release. To the best of our knowledge, no studies have reported the use of carboxylated lignin in paracetamol tablet manufacturing and its effect on the release. Three different formulations have been considered, first one without lignin, second one using pure lignin and the third one contains carboxylated lignin. Paracetamol is utilized as a model drug in this research, it is a nonsteroidal anti-inflammatory [35]. Paracetamol is widely used as a pain relief drug with a fast absorption within the small intestine of the human body [36,37]. Tablets were prepared by direct compaction and characterized using disintegration and dissolution tests. Modified lignin was verified using Fourier-Transform Infrared spectroscopy (FTIR). Drug release rates were measured using dissolution tests at pH 5.8 according to United States pharmacopeia (USP) [38]. In order to investigate the controlled release behaviour of paracetamol, dissolution tests were carried out at acidic condition (pH 1.2) and phosphate (pH 7.2) buffer solutions.

2. Experiments

2.1. Materials and methods

Paracetamol (4-acetamidophenol, Phion) was used as a model API to prepare three different formulations. Microcrystalline cellulose (MCC SANAQ® 101 L USP/NF/EP) and Alcell lignin (Tecnaro (Ilsfeld, Germany)) were used as excipients. More details on the lignin used in this study can be found elsewhere [2,15]. Table 1 shows the composition of the three formulations considered.

Table 1. Various formulations used in this study.

	Formulations		
Material	**A**	**B**	**C**
Paracetamol (% wt.)	20	20	20
Alcell lignin (% wt.)	0	10	0
Modified Alcell lignin (% wt.)	0	0	10
MCC 101 (% wt.)	80	70	70

2.2 Lignin modification

In order to allow conjugation reactions between lignin and paracetamol, lignin is functionalized with carboxylic acid groups. Synthesis of COOH-lignin involves ring-opening reaction of succinic anhydride with 4-dimethylaminopyridine (DMAP). 2 g of lignin, 2 g of succinic anhydride and 400 mg of DMAP were added to 250 ml of tetrahydrofuran (THF) in a 500 ml round-bottom flask, followed by stirring for 48 hr at room temperature [18]. The obtained carboxyl functionalized precipitate was filtered, and then, washed for 24 h using deionized water via soxhlet extraction system in order to remove the unreacted reagents. Finally, the modified lignin was placed in a freeze-dryer overnight. The proposed mechanism pathway [18] is presented in Fig. 1.

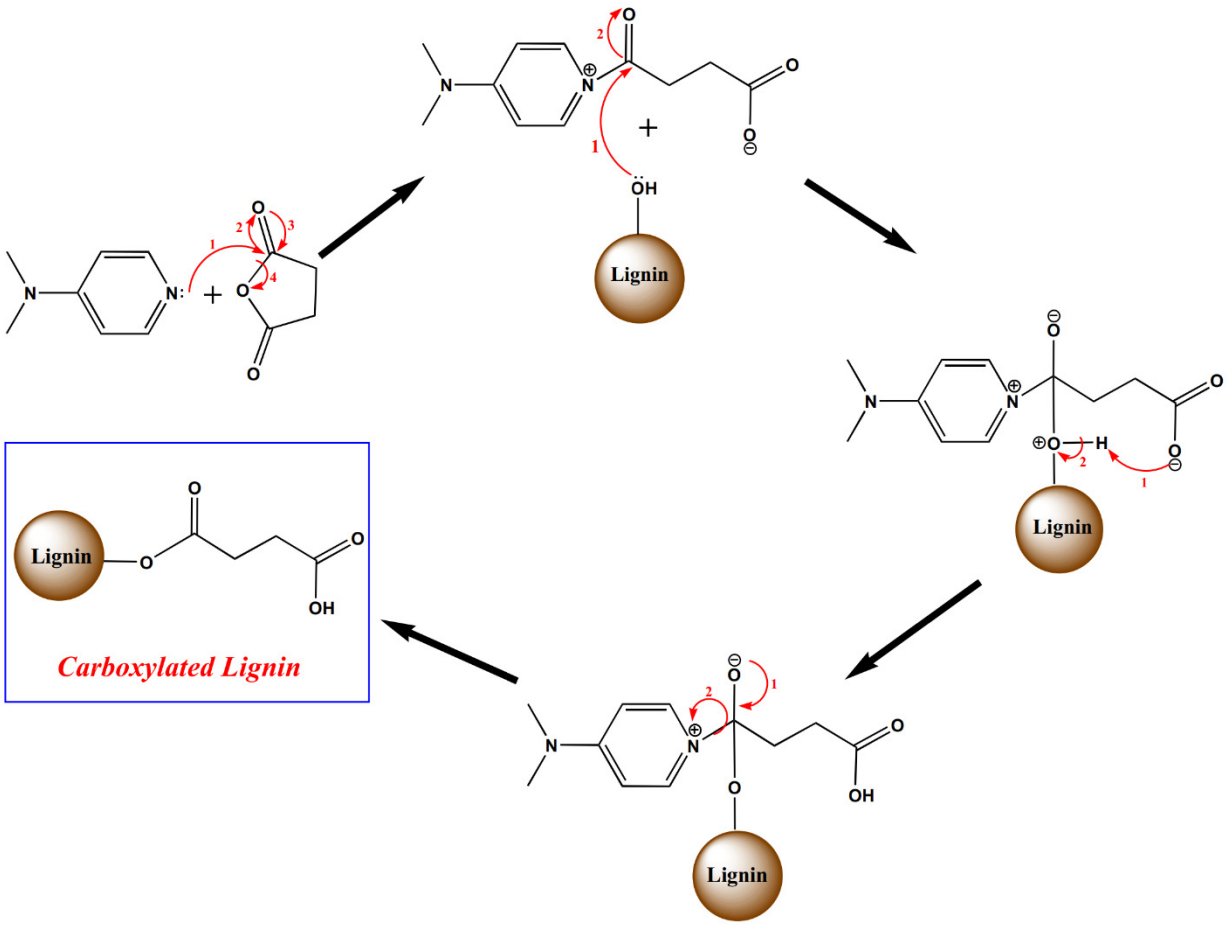


Figure 1. Mechanism of lignin carboxylation.

2.3. Tablets preparation

In order to prepare tablets, a single-punch tablet press (Gamlen Tableting GTD-1 D series, UK) was utilized. 100 mg of each formulation were compacted to make each tablet in a 6 mm die. The tablet load was set at 400 kg, with compaction rate of 180 mm/min.

2.4. Characterisation

Fourier transform infrared spectroscopy (FTIR, ThermoFisher, Ireland) measurements was carried out utilizing a Nicolet Nexus FTIR spectrometer between 450–4000 cm−1 equipped with an attenuated total reflectance accessory (ATR), a total of 60 scans with a spectral resolution of 2 cm−1. Tablet hardness was measured using a tablet hardness tester, Pharma Test (PTB 311E 3 in 1 hardness, diameter and thickness tester, Hainburg, Germany). Pharma Test PTZ-DIST- Disintegration Test

Instrument (Hainburg, Germany) was used to measure the tablet disintegration time. 900 mL of deionized water was filled out the apparatus vessel and the peddle speed was kept constant at 100 rpm. The temperature of vessel was adjusted at 37˚C. The tests were performed for those two formulations containing pure lignin and carboxylated lignin until the tablets completely disintegrate. A Pharma Test PTWS 120D 6-Station Tablet Dissolution Testing Instrument (Hainburg, Germany) was utilized to analyse the tablets dissolution rate. For drug concentration measuring, Cary 60 UV Spectrophotometer (Agilent Technologies, Waldbronn, Germany) was used in 249 nm wavelength. All the tests were carried out in triplicate. The calibration graph can be found in Supplementary Information.

2.5. Dissolution test procedure

Phosphate buffer with pH=5.8 (according to USP 23) was used as dissolution medium [38,39]. 900 mL of medium was prepared to fill each dissolution vessel. The temperature of medium chamber and the stirrer speed were considered to keep constant at 37 ± 0.5˚C and 50 rpm respectively. For running the dissolution test, first, the temperature should reach to 37˚C. For each run, three vessels were utilized and one tablet was considered for each vessel. Five mL of sample were withdrawn at 5, 10, 20, 30, 40, 50, 60 and 120 minutes from each vessel and the same amount of medium was supplant, instantly. Afterwards, the samples were filtered applying Captiva Econofilters (PTFE membrane, 13 mm diameter, 0.2-µm pore size. Eventually, all samples were analysed to measure the drug concentration using Cary 60 UV Spectrophotometer at 249 nm wavelength, which was calibrated to find the wavelength. The cuvette type was 1/Q/10, quartz with pathway of 1cm. In order to minimize the statistical error, all the experiments were done in triplicates. For the dissolution tests of pH-responsive analysis, due to the evaluation of the controlled release behaviour of paracetamol in carboxylated lignin formulation, two different pHs were considered, phosphate buffer solution, pH=7.2 (intestine environment) and acidic buffer solution (0.1 N HCL), pH=1.2 (gastric environment) [40,41].

3. Results and discussion

3.1. FTIR characterization of pure lignin and modified lignin

The FTIR spectra analysis was carried out to monitor the pure lignin structure and to characterize the chemical changes in the functional groups of lignin structure during the carboxylation reactions. Fig. 2 shows the spectra of pure lignin and functionalized lignin, which have similar peaks such as; C=O (carbonyl groups) at 1600 cm-1, –OH (hydroxyl groups) which are attributed to the phenol and alcohol in the region of 3600–3100 cm-1 and aromatic ring region at 1425-1514 cm-1. Nevertheless, hydrogen-bonded hydroxyl stretching band of carboxylic acid (2250–3600 cm−1) and the stretching vibrations of C=O of the unconjugated –COOH groups at 1720 cm-1 exhibit a stronger absorption bond than the pure lignin (unmodified), proving that grafting lignin with carboxylic acid groups has been successfully done.

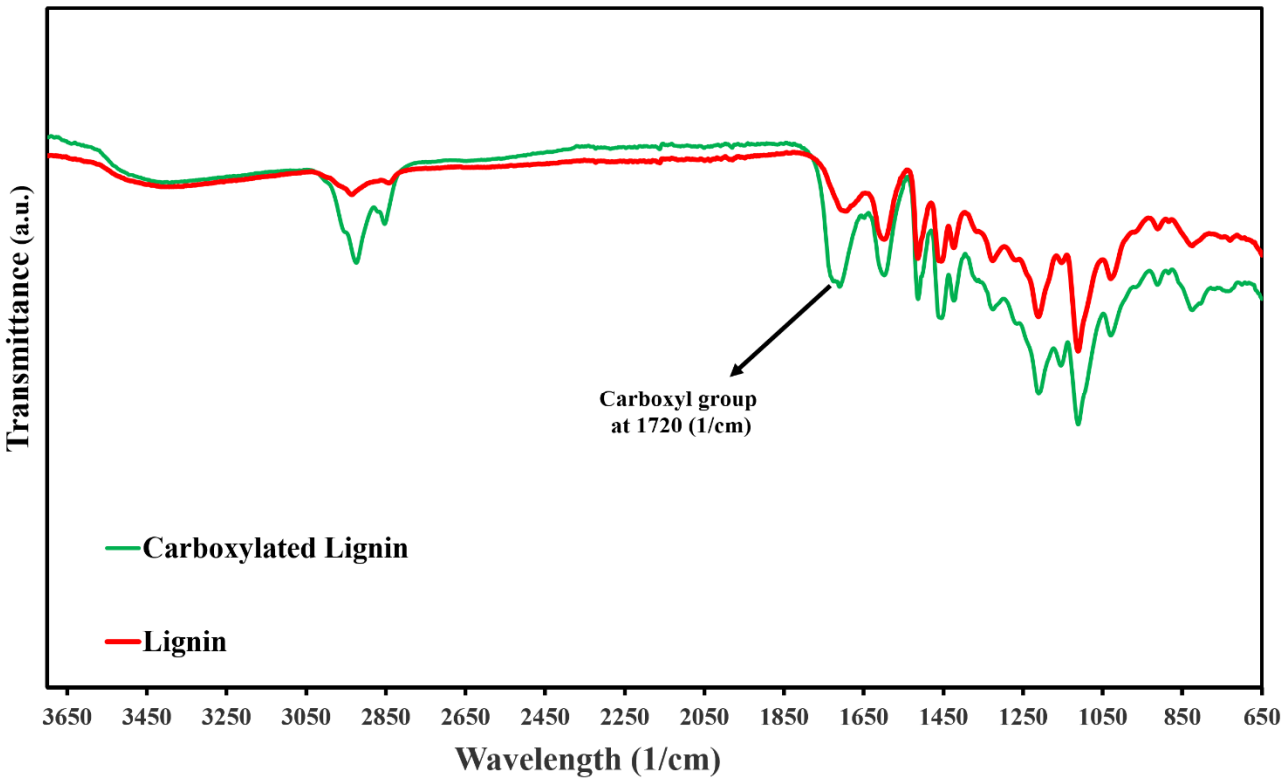


Figure 2. FTIR spectra of lignin (red) and carboxylated lignin (blue).

3.2. Effect of lignin carboxylation on the tablet disintegration time

Tablet disintegration time effect the tablet dissolution and can be used as a valuable test for solid oral dosage forms. Tablet hardness can influence tablet disintegration time, which higher hardness leading to longer disintegration times [42,43]. In order to study the effect of lignin carboxylation on the tablet disintegration time, disintegration test was performed for three different tablets, non-lignin, pure lignin and modified lignin. Fig. 4 presents the disintegration time results; in which faster disintegration time for tablets containing modified lignin is obtained. Moreover, tablet hardness is measured using a hardness tester (pharma test, PTB) for three formulations, and the results show higher hardness with the formulation without lignin (Fig. 3). Tablet hardness is affected by physical properties of materials, and interaction of drug with excipient. The tableting method is the same for each formulation, in order to mitigate its influence on tablet hardness. Generally, lower hardness equals to higher porosity, therefore, the lower hardness or higher porosity of carboxylated lignin tablet is due presumably to the structural differences in lignin after modification.

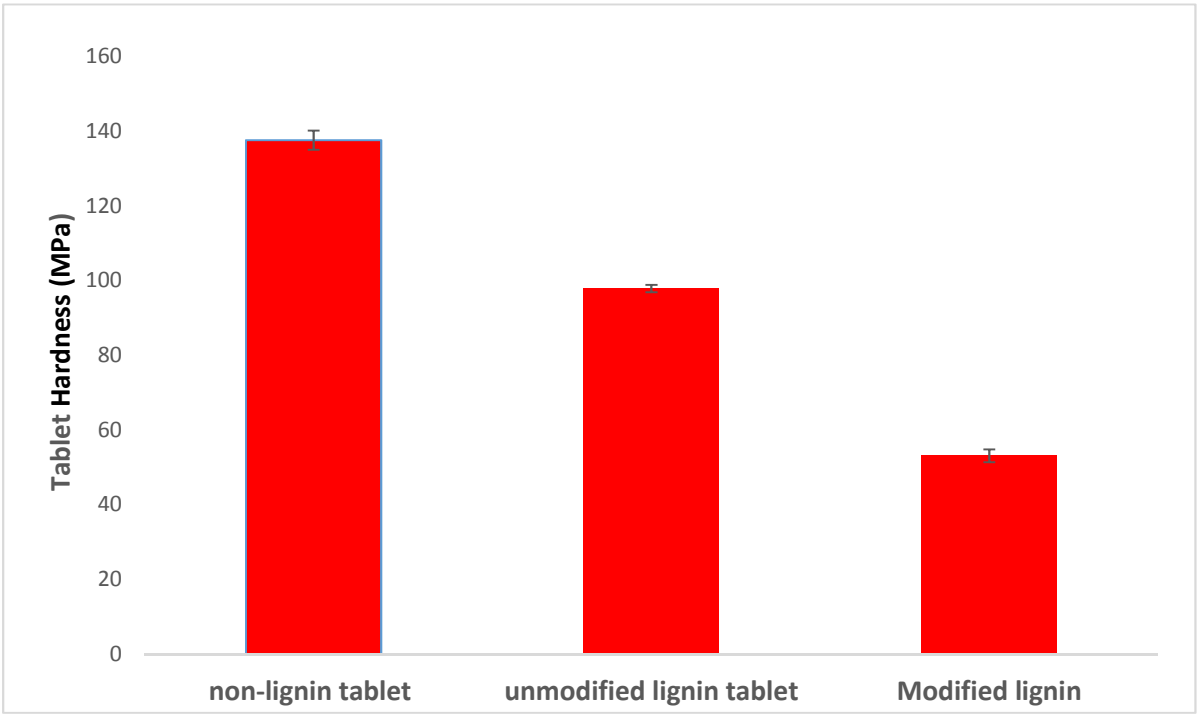


Figure 3. Hardness of tablets prepared contain pure lignin, modified lignin and non-lignin tablet

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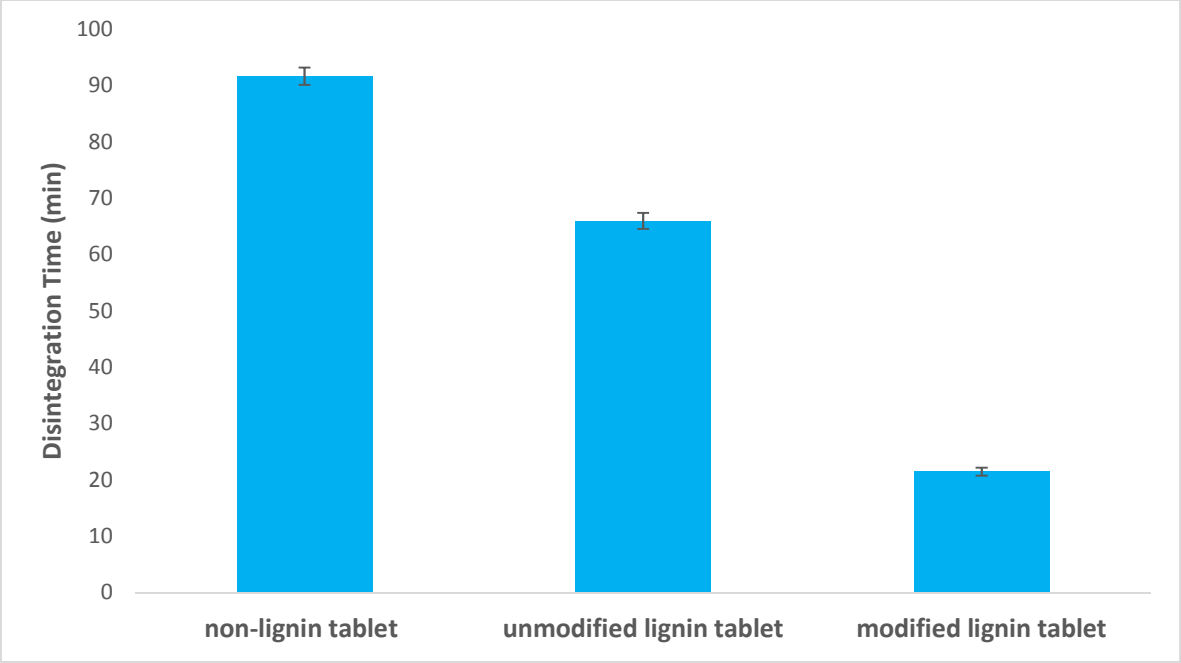

Figure 4. Disintegration time of tablets prepared contain pure lignin, modified lignin and non-lignin tablet.

3.3. Effect of lignin carboxylation on drug release rate

Dissolution tests were performed to evaluate the effect of lignin and carboxylated lignin on the paracetamol tablet release rate. The three different formulations in table 1, were considered to study paracetamol release rate in phosphate buffer solution at pH 5.8, according to USP [38]. The release graphs of three different batches of paracetamol are displayed in Fig. 5. Interestingly, the graphs illustrate that the tablets containing functionalized lignin has the highest drug release rate and this correlates with the faster disintegration time of these formulations and lower tablet hardness. In addition, the dissolution release is attributed to formulation and material properties.

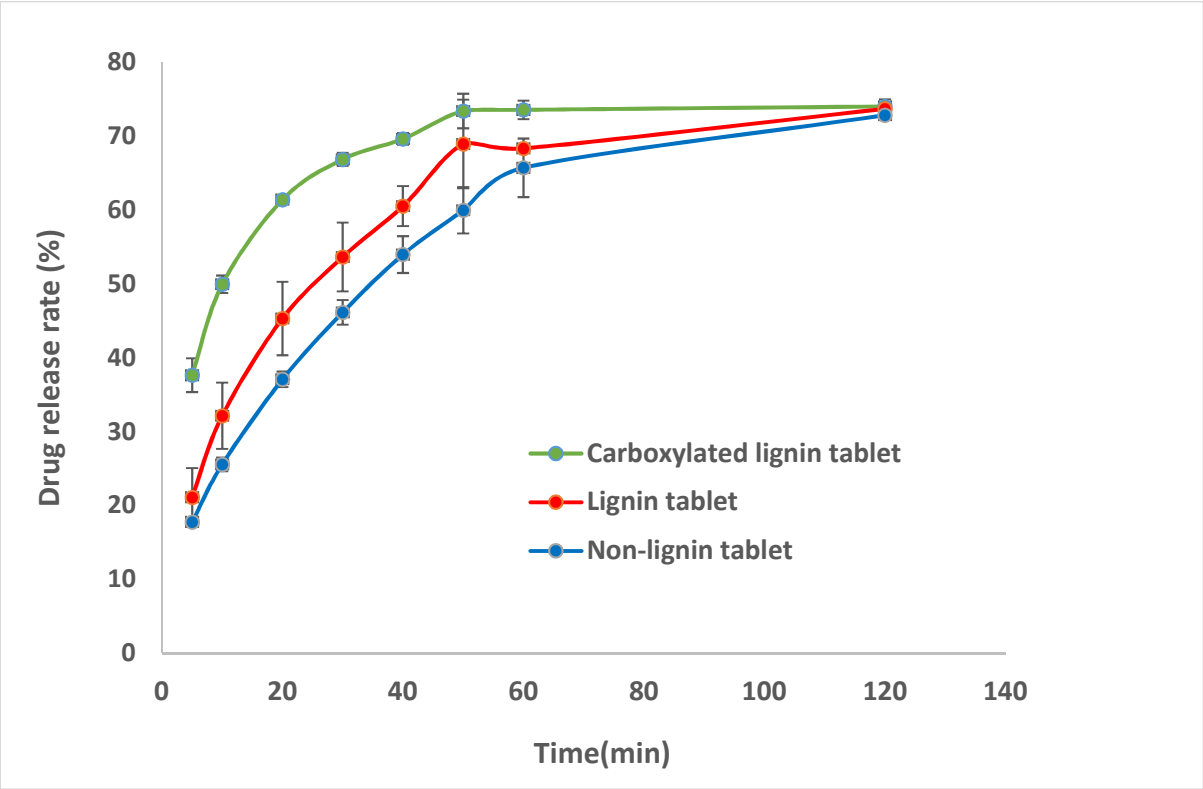

Figure 5. Drug release rate of paracetamol for the formulations at pH=5.8.

Moreover, the prepared tablets containing pure lignin have the higher drug release rate compared to formulation without lignin due to faster disintegration and lower tablet hardness [9]. Thus, Lignin functionalization improved the release properties of directly compacted paracetamol tablets.

3.4. Controlled release and pH-responsive behaviour of carboxylated lignin

The pH-responsive behaviour of carboxylated lignin was investigated using dissolution tests in different media at various pH values, 0.1 M HCL solution (pH of 1.2, gastric environment) and phosphate buffer (pH 7.2, intestine environment) at 37˚C. The dissolution graphs in Fig. 6 presents the greater release rate of drug in buffer with pH=7.2 [40]. Increasing the carboxyl groups results to increase drug release at pH=7.2 compared to pH=1.2. In pH=1.2, the electrostatic repulsion between lignin carboxyl groups decrease due to protonation of carboxyl groups at lower pH values. However, in pH=7.2, due to ionization of carboxyl groups (Pka =4.8) of modified lignin the negatively-charged ions repel each other and presumably this leads to an swelling effect similar to how hydrogels swell on ionisation [44] and this results in higher release rates of API. The drug release rate was studied in

our previous work by adding lignin in the formulation [9]. The results showed higher drug release rate for formulation containing lignin. The results of this work reveal that lignin as natural biopolymer is a promising compound for using in controlled release system and also for enhancing the solubility of active pharmaceutical ingredients.

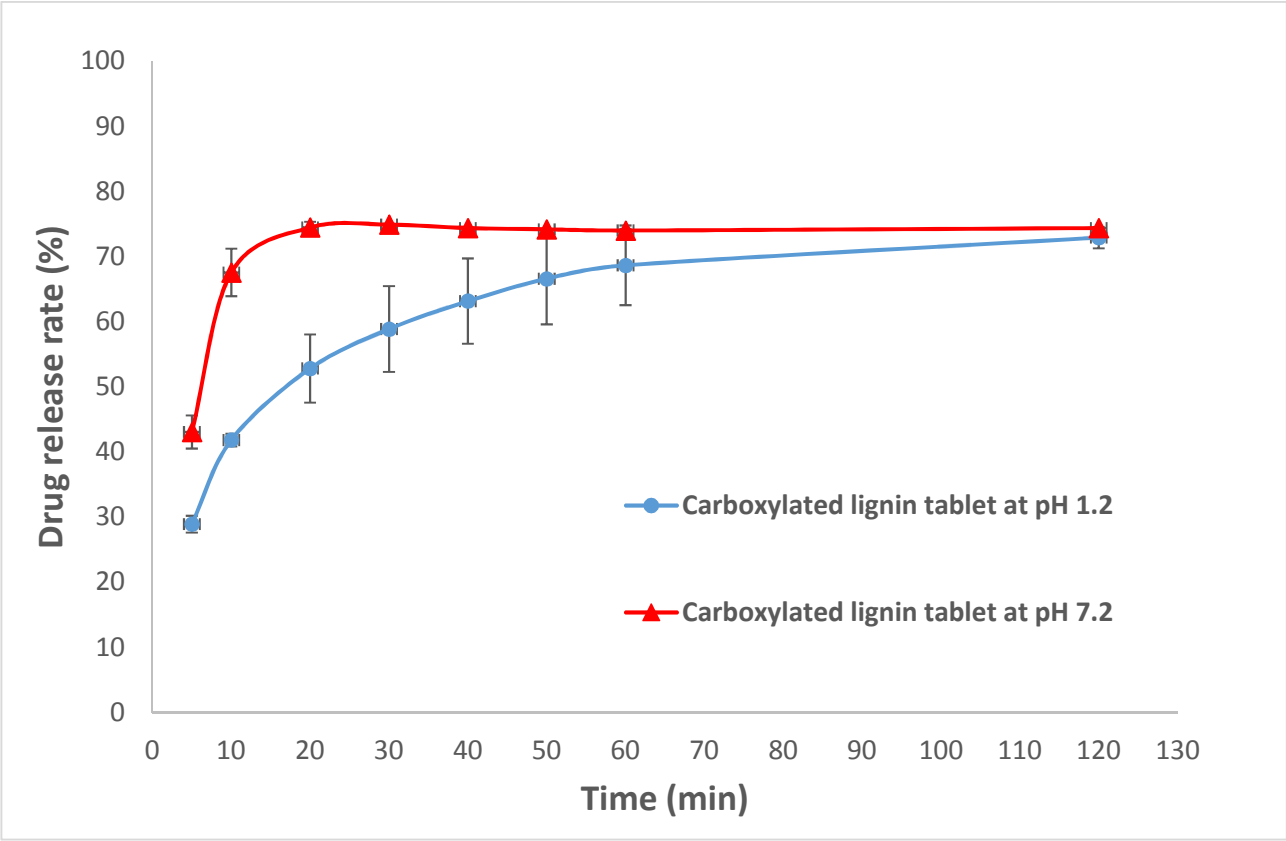

Figure 6. Drug release rate of carboxylated lignin in pH=1.2 and 7.2.

4. Conclusions

The aim of the present study was to evaluate the pH-dependent releasing behaviours of modified lignin and the effect of lignin modification on the drug release rate. Lignin modification was conducted via carboxylation of lignin functional groups. In order to analyse the carboxyl groups in lignin and carboxylated lignin structure, FTIR test was carried out and the results displayed a successful carboxylation. The dissolution results illustrate that there is a higher release rate of paracetamol from carboxylated lignin tablets, and this is attributed to the lower degree of interaction between lignin and the API due to the deprotonation of -COOH groups from modified lignin. Furthermore, controlled release behaviour of carboxylated lignin was performed in gastric pH of 1.2

and intestine pH of 7.2 and the release results presented successful properties of controlled release. Additionally, the tablet disintegration tests showed the faster disintegration time with the carboxylated lignin tablets compared to pure lignin tablets due to lower hardness of tablets with modified lignin. Thus, these investigations presented a successful use of carboxylated lignin natural biopolymer as excipient in oral dosage forms for desired drug controlled release.

Acknowledgements

This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750.

The authors also would like to thank Mr. Rahmatullah Shaikh, Department of Chemical Sciences, Bernal Institute, Synthesis and Solid State Pharmaceutical Centre (SSPC), University of Limerick, Limerick, Ireland, for his useful comments on the UV calibration.

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Chapter 5.

Conclusions and future work

Conclusions

An experimental investigation has been performed that focused on the effect of using Alcell lignin in formulations and its influence on granules properties and drug release behavior.

Chapter 1 introduced a fundamental study on the powder and granule behaviour during dry granulation by roll compaction process. Different formulations are considered using various excipient in order to characterize excipients properties and their effect on the formulation behaviors. The relation between critical process parameters (CPPs), including roll pressure, screw speed and critical quality attributes (CQAs) including ribbon density and granule size (D50) are mapped using JMP software to develop a process map. The results illustrated the statistically effect of roll pressure on the ribbon density and D50 of granules. On the other hand, the effect of screw speed was negligible.

The results show that a variation in roll pressure has a considerable effect on ribbon density and granule size (D50) in the roller compaction process. At higher roll pressure and constant screw speed, the amount of powder between rolls are constant and more pressure leads to more densification of powder, especially for smaller particle sizes, cohesive and compressible powders, which results in a higher density and larger D50 of granule size. On the other hand, it was found that screw speed does not have any significant effect on critical quality attributes of products; however, it affects other process variables such as the amount of powders, roll gap, and residence time of powders between rolls.

Another important objective of this study was to investigate the capability of Alcell lignin as a natural polymer to use as an excipient to improve powder properties, costs and delivery of tablets as final products. Alcell lignin, as a natural polymer can improve granulation process because of good flowability, low cost and ease of availability. Interestingly, it was revealed that less operational limitations were observed when lignin was introduced as an excipient in the formulations.

Specifically, the work shows:

- The relation between critical process parameters (CPPs) and critical quality attributes (CQAs) by process map

- The significant effect of roll pressure as a key process parameter on the ribbon density and granule size (D50)
- The influence of Alcell lignin as an excipient to improve powder and granule properties in different formulations
- The applicability of NIR spectroscopy as a PAT tool for on-line measurement of ribbon density in roll compaction process

Chapter 2 focused on the effect of lignin-based excipients on the release rate of oral dosage aspirin tablets. In this study, Alcell lignin is used as an excipient to show the effect of natural polymer on the drug release rate. Dry granulation by roll compaction was used to prepare tablets. Lignin was selected as an excipient to evaluate its influence on release rate and tablet properties at varying processing conditions due to its chemical structure. Different formulations are considered to compare the effect of lignin on the API release rate. Results illustrated that lignin tablets compared to non-lignin tablets have higher hardness, faster disintegration time, and higher release rate. Indeed, the critical quality attributes of the tablets were improved by introducing the lignin. Higher release rate of tablets with lignin formulation are due to the amorphous structure of lignin and interaction with the API, which improves drug solubility and therefore bioavailability, the key factor in oral dosage development. On the other hand, higher roll pressure leads to more densified ribbons associated with lignin blends and consequently, larger granules are produced. These larger granules result in porous tablets, which leads to faster disintegration times as solvent diffuses faster into the tablets. Also, greater hardness for the tablets containing lignin is attributed to better affinity between lignin and MCC which leads to lignin acting as a tablet binder.

The work shows:

- Higher drug release rate by adding lignin as an excipient in the formulation
- The effect of roll pressure as key process parameters on the tablet disintegration time
- The use of lignin as an excipient in oral dosage form

In chapter 3, the work focused on the design and prediction of drug release rate using artificial neural network (ANN) model considering two hidden layers and combining various activation functions, i.e. linear, hyperbolic tangent, and Gaussian. Two formulations, one containing lignin, and the other one without lignin were considered to investigate the effect of lignin on the API release rate. The tablets were prepared using dry granulation method followed by milling and tableting. A new formulation containing lignin was designed in this work to enhance the bioavailability of poorly soluble water drugs. The results of release rate indicated that the tablets containing lignin have higher release rates of API. The results of ANN modelling revealed that the developed model can predict the release rate with high accuracy and R^2=0.99 was obtained for most cases. The model was used to predict the kinetics and equilibrium of the release rate and consensus was obtained between the predicted and measured data. The validated model was then used to understand the effect of process parameters on the release rate, and it was revealed that increasing roll pressure decreases the release rate, because larger granules are produced which in turn results in lower release rate.

The works show:

- The effect of lignin on the API release rate using ANN model
- The effect of roll pressure as a process parameter on the drug release rate
- Higher roll pressure resulted in larger granules and decreased the drug release rate

The work in chapter 4 introduces the lignin functionalization to use as an excipient in oral dosage formulation in order to investigate the effect of that on pH-sensitive behavior and release rate of drug.

Lignin modification was conducted via carboxylation of lignin functional groups. Interestingly, the dissolution results illustrated higher release rate of paracetamol with the carboxylated lignin tablets, which is attributed to the enhancement of electrostatic repulsions between -COOH groups of modified lignin and functional groups of paracetamol. Furthermore, controlled release behaviour of carboxylated lignin was performed in gastric pH of 1.2 and intestine pH of 7.2 and the release results presented successful properties of controlled release. Additionally, the tablet disintegration tests

showed faster disintegration with the carboxylated lignin tablets compared to pure lignin tablets. Thus, these investigations presented a successful use of lignin as an excipient in oral dosage forms for desired drug controlled release.

The work shows:

- Lignin cab be functionalized by increasing the carboxyl groups in lignin structure
- pH- responsive behaviour of drug release through the addition of modified lignin in the oral dosage formulation
- Drug release enhancement is attributed to:
  - The faster disintegration time of these formulations and lower tablet hardness.
  - The increase in the ionization degree of carboxyl functional groups in carboxylated lignin tablet compared to lignin and non-lignin containing tablets and the electrostatic repulsions of functional groups in drug molecules (hydroxyl and amides) and –COOH of modified lignin lead to a burst-release of drug.

Future work

The main issue in the pharmaceutical industry is to improve drug delivery and drug release rate. PH-responsive behavior of drugs is a big challenge to improve, especially in cancer disease. Recently, many researchers are focused on these challenges using natural biopolymers due to their biocompatibility and biodegradability properties [1, 2, 3, 4, 5 and 6].

Upgrades are:

- To look into whole process chain of RC, milling and tableting
- use of X-ray CT to characterise porosity of tablets
- The use of biopolymers to prepare nanocarriers for drug delivery
- Development of continuous manufacturing based on lignin formulation and integrated advanced PAT tools

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Appendix: Published Papers

Powder Technology 341 (2019) 38–50

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Microcrystalline cellulose, lactose and lignin blends: Process mapping of dry granulation via roll compaction

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ARTICLE INFO

Article history:
Received 16 September 2017
Received in revised form 28 May 2018
Accepted 2 July 2018
Available online 3 July 2018

Keywords:
Dry granulation
Roll compaction
Critical process parameters
Critical quality attributes
Quality by design
Process map
Natural excipient
NIR spectroscopy

ABSTRACT

In this study, a process map was developed in an effort to improve the understanding of dry granulation of pharmaceutical excipients by roll compaction process, and to implement the quality-by-design (QbD) approach. Through development of the process map, a correlation was made between the critical process parameters (roll pressure, screw speed), and critical quality attributes (density of ribbons and granule size). This method reduces development time, quantity of materials required and cost. A new excipient formulation based on natural polymers (lignin and cellulose) was utilised to improve the properties and reduce costs associated with tablets production. A variety of lignin, microcrystalline cellulose (MCC) and lactose monohydrate formulations were compacted followed by milling to obtain granules. Formulations were also characterised in terms of compressibility and flowability. Density of ribbons as well as granule size distribution were mapped versus critical process parameters. Based on this work as initial study, roll pressure was found to be a critical process parameter, higher ribbon density and larger granule size obtained with higher roll pressure. It was also revealed that the process map is a powerful tool in understanding the dry granulation, and can be used to construct a design space for pharmaceutical manufacturing.

1. Introduction

The current practice in pharmaceutical manufacture is batch wise in which trial and error approach, which is time-consuming and wasteful is used for new formulations and equipment. Recently, continuous processing has received more attention in the pharmaceutical industry as it offers superior characteristics compared to batch processing [1]. Upon developing continuous processing, we can avoid scale-up issues, reduce cycle times, variability and production costs, ensure faster product release, increase flexibility and efficiency, and improve product quality [2, 3]. Underpinning research is required to transform batch mode operation to the continuous mode. One of the key processing steps in the pharmaceutical manufacturing is granulation, as the properties of final products are dependent on the granule properties. In the manufacturing process, active pharmaceutical ingredients (API) and excipients mixtures are granulated to improve flowability and content uniformity of the particles. There are two main methods for granulation of pharmaceutical formulations, namely dry and wet granulation [4, 5]. In wet granulation, liquid binders are used to form granules from fine powder, whereas in dry mode no binder is required. Indeed, dry granulation is useful for compounds that are sensitive to heat and moisture [6–8]. Roll compaction (RC) is widely used for dry granulation as a continuous process, and has shown more advantages, for example, a reduction in powder segregation and increasing bulk density [7, 9–11].

During roll compaction, fine powder is compacted between two counter-rotating rolls to produce ribbons (briquette) by applying hydraulic force on powder. The ribbons are milled to produce granules, and then compacted to form tablets [11, 12]. As such, controlling ribbon density and granule size are critical in RC process. Therefore, application of RC would promote the paradigm of continuous pharmaceutical manufacturing. In order to develop a continuous line for manufacturing of solid-dosage forms, the process understanding is of great importance so that the critical quality attributes of products are correlated with the process parameters and material properties [13–16].

The mechanism of the dry granulation process is still not well understood in the continuous pharmaceutical manufacturing context. Several models have been deployed such as Johanson model, slab method, finite element method, discrete element method and artificial neural network to correlate the process parameters with ribbon density. These models are of mathematical basis and are used to predict process variations [8, 11–13, 16, 17]. In addition, several researchers have studied different

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https://doi.org/10.1016/j.powtec.2018.07.003
0032-5910/

aspects of RC to understand the effect of process parameters on ribbon density [18–23].

McAuliffe et al. [24] studied the effect of roll pressure on density of ribbons prepared with a formulation containing MCC 102, anhydrous lactose, and they highlighted the impact of roll pressure on ribbon and granule properties at constant screw and roll speed with variable roll gap. They mentioned increasing the roll pressure causes decrease in the roll gap. In addition, it was shown that increasing the roll pressure, have a significant effect on ribbon and granule properties. Souihi et al. [25] investigated the influence of process parameters on ribbon density using the Johanson model for the formulation containing paracetamol, mannitol, and MCC 102. They mentioned that Johanson model describes the effect of roll pressure and screw speed on ribbon density and emphasised the minor effect of roll gap on ribbon density compared to roll pressure. Khorasani et al. [21] also studied the effect of roll pressure and roll speed on ribbon density utilising a formulation containing MCC 101 and acetylsalicylic acid with the constant roll gap. Moreover, the screw speed was adjusted automatically to keep the roll gap constant. It was also shown that increasing the roll pressure leads to increase the ribbon density and granule size. On the other hand decreasing the roll speed results in increasing ribbon density and granule size due to increased residence time of powder between rolls. Kumar et al. [26] studied the influence of process parameters on quality attributes of the wet granulation process by developing a regime map for a formulation consisting of α-Lactose monohydrate and PVP. It was shown that the regime map provides a design space for optimisation of granulation. Sajjia et al. [2] analysed the effect of process parameters on ribbon density using of MCC 102, and further explained the effect of roll pressure and screw speed on ribbon density. They believed that increasing the roll pressure leads to ribbons with higher density. They further highlighted the unstable and minor effect of screw speed on ribbon density.

As mentioned, different researchers have studied the effect of process parameters on ribbon density and particle size of granules, but development of a comprehensive process map, which is capable of providing a design space for roll compaction process, is of great importance. Furthermore, the effect of formulation on the ribbon and granule properties has not been studied. None of these investigations have shown the correlation between process parameters and quality attributes by mapping the process, and understanding the influence of material formulation.

Indeed, a comprehensive understanding the process for various formulations is of great importance. In order to determine the best design space in dry granulation processing, one may need to use a wide range of DoE (design of experiments) to fully understand the effect of underlying parameters on ribbon properties as well as granule size. Development of a design space for dry granulation can be achieved with a process mapping, which correlates the process input to the outputs for a wide range of formulations. Recently, several researchers have attempted to show the importance of identifying the interaction between process parameters of materials and quality attributes of products for roll compaction process. They have utilised dimensionless variables for roll compaction, and regime maps for wet granulation processing have been investigated [15, 23, 26–28]. The process map has been successfully developed for wet granulation via twin-screw extruder [26], and it was shown that the process map concept is of great importance for the development of continuous manufacturing. Therefore, it would be of great importance to develop a process map for dry granulation by roller compactor considering new formulations.

Lately, due to different issues in terms of side effects and drug release, use of natural polymers has attracted much attention on the development of tablet formulations through usage of new excipients. Natural polymers offer a number of advantages as excipients in tablet manufacture including; low or no toxicity, regulatory compliance and stability, while enhancing the physicochemical properties of powders and increasing drug release rates. Due to the high chemical functionality of lignin, it can be introduced as a novel excipient for development of new materials [29–37].

In the present study, a process map has been developed for RC processing with various formulations including the novel lignin excipient. Different formulations with differing percentages of microcrystalline cellulose (MCC), lactose and Alcell lignin were designed and used throughout the experiments. For designing the process map, a correlation between input variables including roll pressure, screw speed, and ribbon properties such as density as well as D50 of granules was found. This method reduces development time, quantity of materials and cost. It should be noted that these process maps are a preliminary study and are limited to the specific type of formulations and equipment used in the experimental design. Moreover, in order to assess the applicability of NIR spectroscopy as a PAT tool for on-line monitoring of RC, the density of ribbons containing bio-based materials were analysed using the NIR method. However, it was conducted as an off-line experiment and for limited samples.

2. Experimental procedure

2.1. Materials and methods

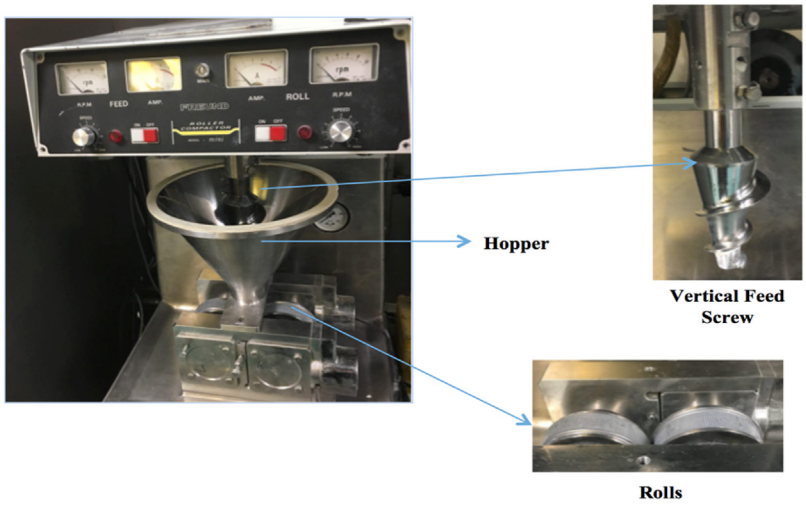
Microcrystalline cellulose (MCC SANAQ® 102 L USP/NF/EP), lactose monohydrate (Lennox USP, NF, BP, Ph, pure pharma grade) and Alcell lignin (Tecnaro, Ilsfeld, Germany) were used as excipients throughout the experiments. In order to prepare the excipient mixtures, microcrystalline cellulose, lactose monohydrate and Alcell organosolv lignin were mixed with 0.5% w/w magnesium stearate (Sigma-Aldrich), which acted as lubricant. For further details on the lignin used in this study the authors are referred to [38]. Two different formulations were considered, first, MCC was mixed with 5, 10 and 20 wt% of lactose, and then MCC was mixed with 5, 10 and 20 wt% of Alcell lignin. All components were blended using a Morphy Richards Stand Mixer with beater attachment at speed setting 3 (100 RPM approx.) for 15 min.

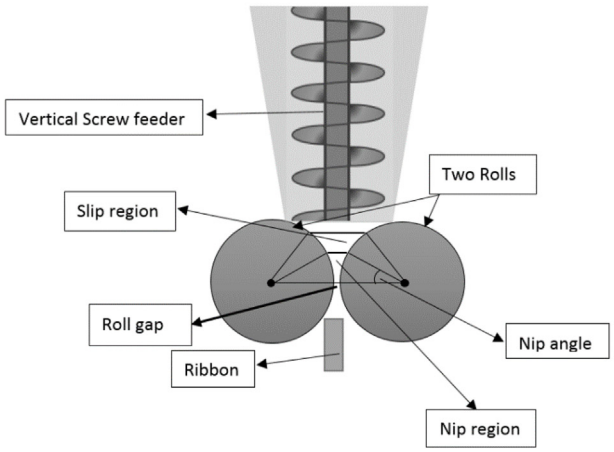
2.2. Equipment and analysis

A top-fed roller compactor "Freund TF-MINI" (see Fig. 1) with a vertical screw feeder was utilised throughout the RC experiments. The width and diameter of rolls were 25 and 100 mm, respectively. The roll speed was set at 4 rpm for all experiments. Process parameters, screw speed (SS) and roll pressure (RP), were changed with variable screw speed (8–18 rpm) by 2 rpm step and roll pressure (10–50 bar) by 5 bar step. An envelope density analyser, (GeoPyc 1360, Micromeritics Instrument Corp., Norcross – USA) was used to measure the ribbon density. The roll gap was uncontrolled and variable during the experiments. The thickness of produced ribbons was measured to be between 1 and 3 mm for all samples.

In addition, a multipoint Near-Infrared (NIR) spectrometer, Multieye NIR, was utilised to characterise the ribbon density. The NIR spectra were calibrated using the density obtained via the GeoPyc instrument and developing a calibration model. Partial Least Square (PLS) technique was used for calibration of NIR results. The produced ribbons were milled with a conical mill (Laboratory Comil 193 AS) with 813-μm mesh size at 3000 rpm mill speed to produce granules.

The particle size distribution (PSD) of powders and post-milling granules were measured using Microtrac S3500 particle size analyser (Malvern). Powder flow and compressive behaviour of materials were evaluated using powder flow rheometer (Freeman Technologies FT4). For characterising the morphology of powders, scanning electron microscopy (SEM) was performed under vacuum. Particle shape and surface morphology of the powders were examined using a scanning electron microscope, (Hitachi TM-1000 desktop SEM). Schematic representation of the roller compactor and the photo of sieve mill and RC are shown in Fig. 1.





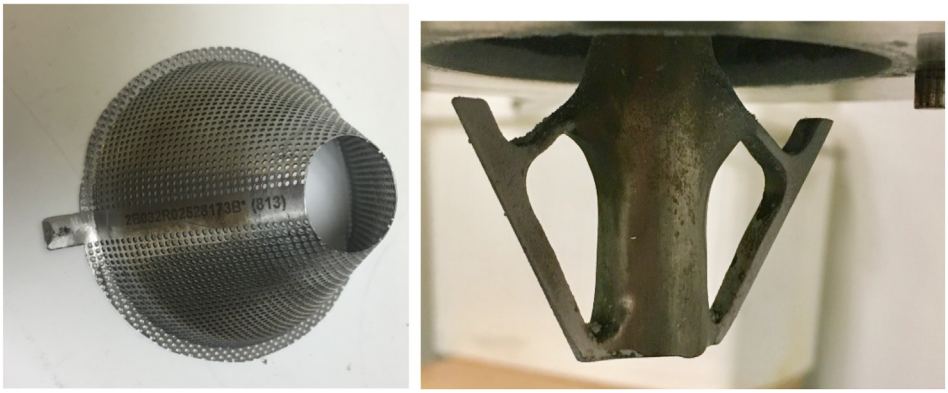


Fig. 1. Freund roller compactor and mill used in experiments.

3. Results and discussions

3.1. Effect of process parameters on ribbon density

In order to implement the quality by design (QbD) approach for roll compaction process, first, a relationship between process parameters and quality attributes of products should be defined. For developing a basic understanding of dry granulation process by roller compactor, the effect roll pressure and screw speed on ribbon envelope density are plotted by using *JMP 12 pro* software and shown in Fig. 2. As expected, the ribbon envelope density is greatly influenced by roll pressure, while screw speed has minor effect on the density.

It should be pointed out that in some cases, insufficient data were collected due to process limitations at these operating conditions. It is observed that applying more roll pressure, at constant screw speed, leads to denser powders, and consequently produced ribbons with higher density for all samples. Higher roll pressure under constant screw speed leads to more compaction between two rotating rolls and thereby higher density of ribbons. In other words, in constant screw speed, the amount of powders and powder residence time between

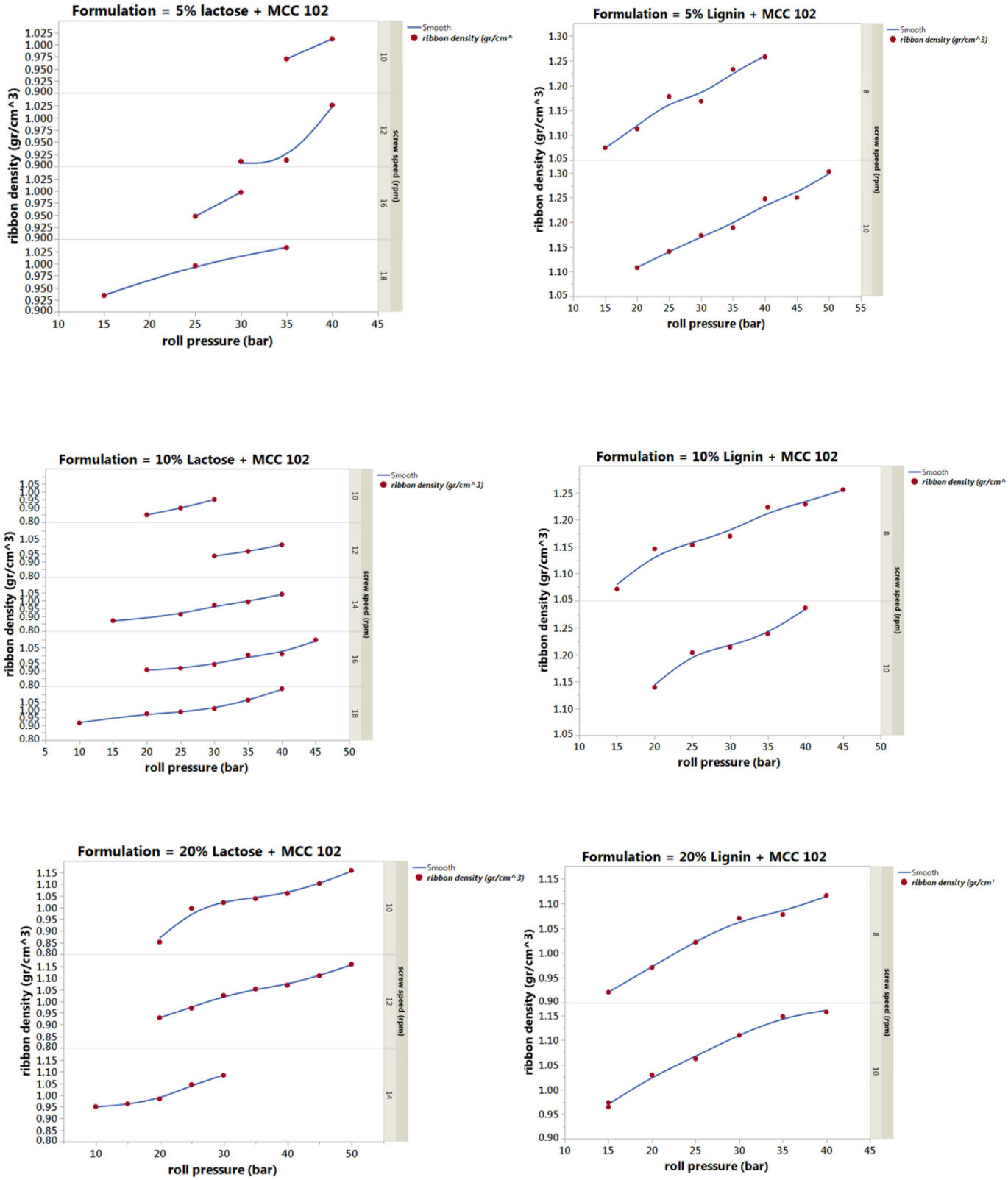
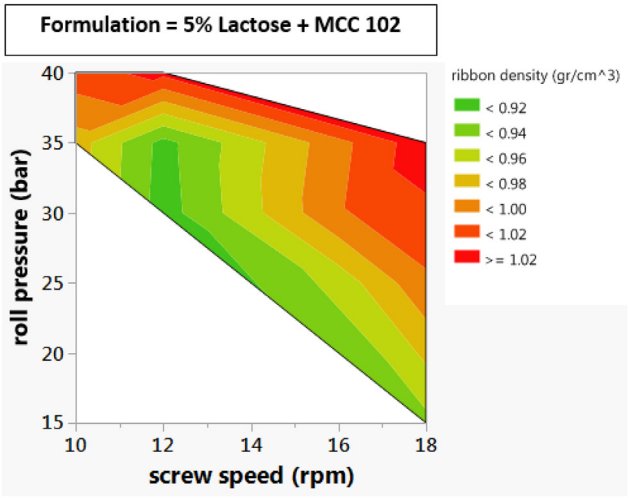
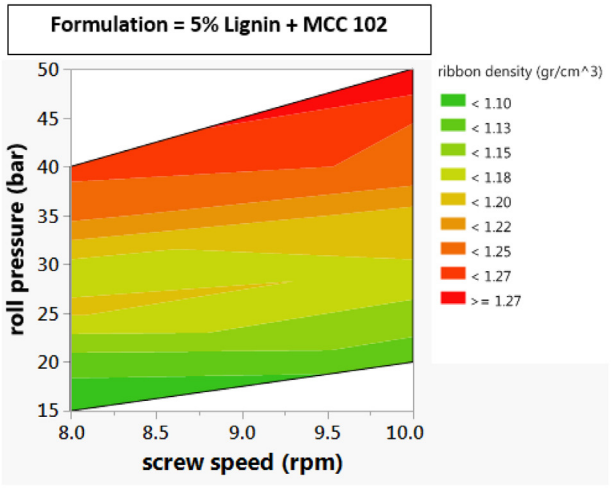


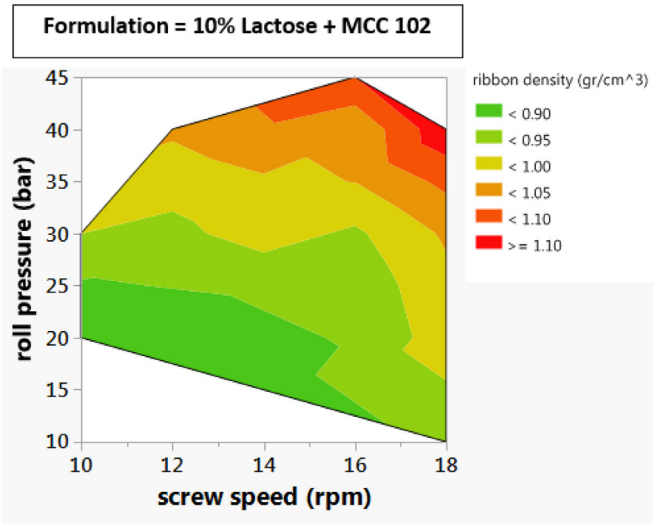
Fig. 2. Effect of process parameters on ribbon density for various formulations.

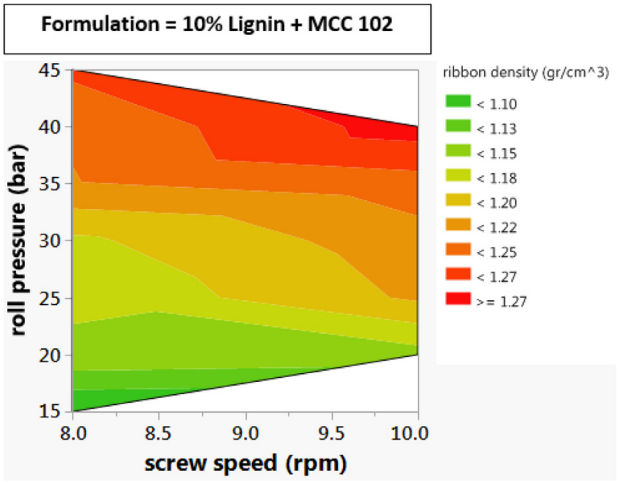
the rolls are constant as well, and more pressure results in more roll force and more densification of ribbons. The graphs of different percentages of lactose illustrate wide range of process parameters, while the graphs with lignin show more limitations in terms of screw speed.

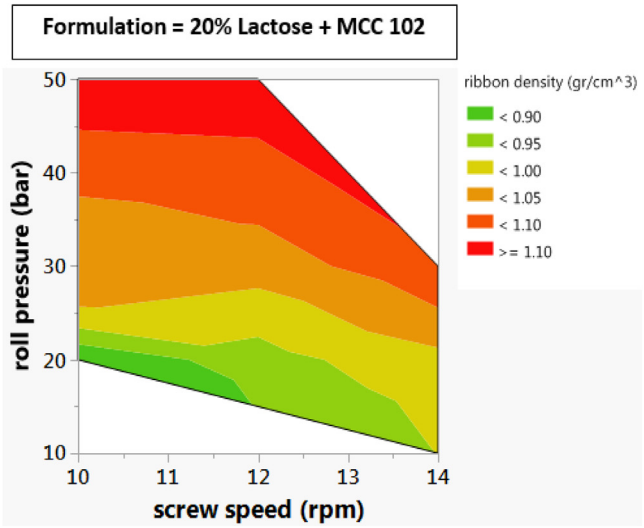
Furthermore, it is observed that at the same content of lactose and lignin in the formulation, higher ribbon density is obtained for the formulation containing lignin, which could be attributed to the intrinsic physical and chemical properties of lignin and interaction with MCC, which will be further investigated in the next section. On the other hand, as it can be seen in Fig. 2, screw speed has a minor influence on the ribbon density for all formulations. For each formulation with the same roll pressure, increasing the screw speed results in increased











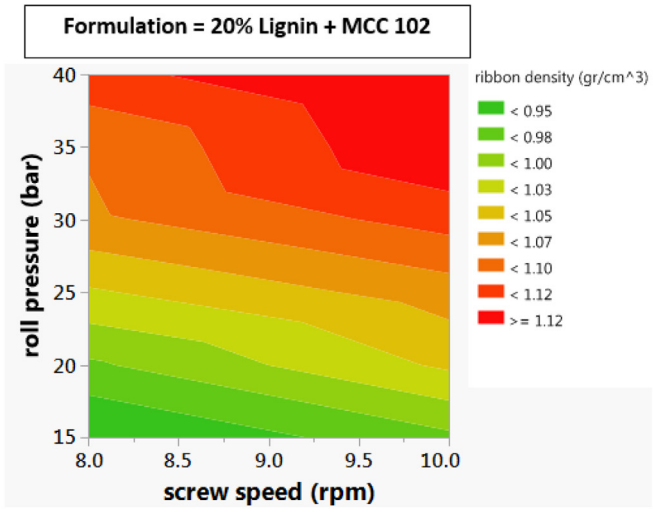


Fig. 3. Contours Plot for Density (g/cc), Formulation = 5, 10 and 20% Lactose.

Fig. 4. Contours Plot for Density (g/cc), Formulation = 5, 10 and 20% Alcell lignin.

ribbon density, although slightly. As shown in Fig. 2, more limitations of process parameters are observed for higher percentages of lactose formulation. The results confirm that lignin is a promising bio-based excipient for tablet manufacturing and almost similar behaviour with common excipients (e.g. lactose) was observed for the formulations containing lignin.

3.2. Effect of formulation on density of ribbons

To investigate the effect of the formulations used on the density of the produced ribbons, contours of density versus roll pressure and screw speed for different formulations are plotted as shown in Figs. 3 and 4. These contours show the two-dimensional colour representation

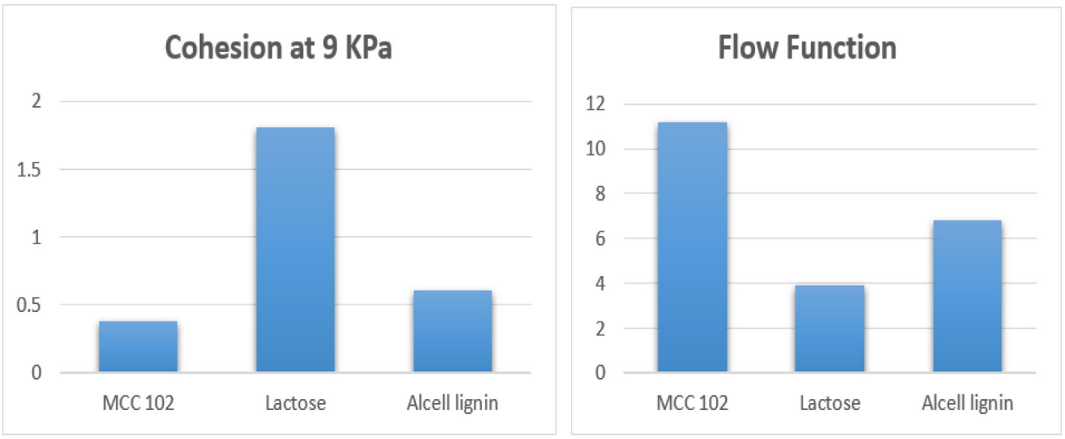


Fig. 5. Cohesion and flow function graphs for Lactose, Alcell lignin and MCC 102 measured by FT4 powder rheometer.

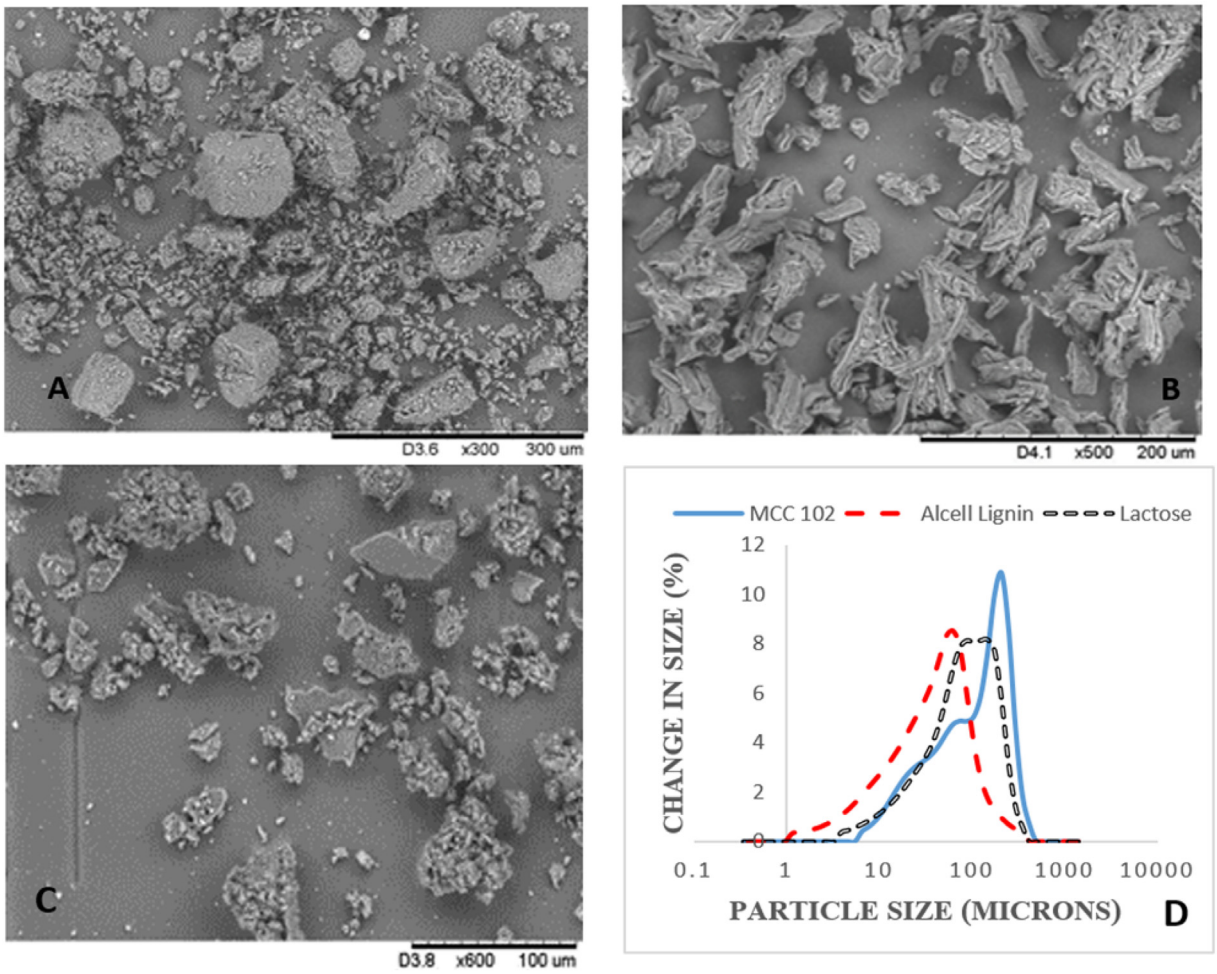


Fig. 6. SEM of Lactose (A), MCC 102 (B) and Alcell lignin (C), and particle size distributions (D).

for the relationship between process parameters specified and the ribbon density.

Fig. 3 shows the contours of formulation with lactose at different percentages in which the white area, at the background of the map, indicates the process limitations. The latter means that the experiments cannot be conducted due to operational problems such as roller blockage, over compaction, etc. In terms of blockage of materials, it happened at the end of screw feeder, the neck of hopper, in the slip region (see Fig. 1). As such, these contours also indicate the workability of RC in which the colour areas correspond to the working conditions of equipment.

It is observed that increasing the percentage of lactose results in higher density and less limitation in the process parameters. Furthermore, by increasing the percentage of lactose, the effects of screw speed on ribbon density decay. At 5% of lactose, increasing the screw speed leads to enhancing the density of ribbon slightly, whereas for

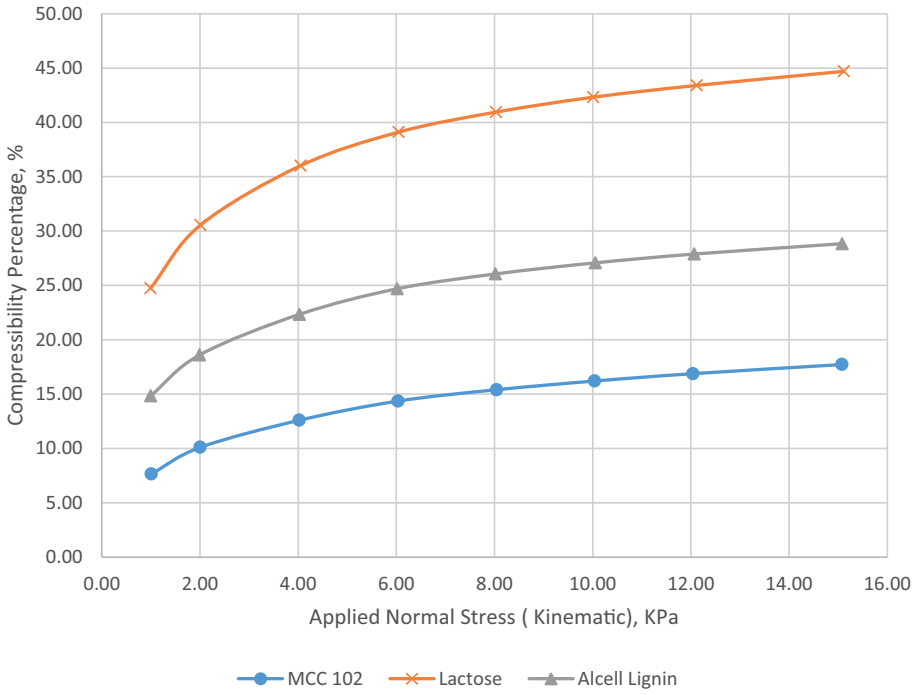


Fig. 7. Compressibility of Lactose, MCC 102 and Alcell lignin measured by FT4 powder rheometer.

10% of lactose, the screw speed influence is slight, and for 20% of lactose it does not have any appreciable effect (see Fig. 3) which is in agreement with literature [8, 24].

Fig. 4 illustrates the contours of formulations with different percentages of Alcell lignin including 5, 10 and 20 wt. percentage. The plots show less limitation in terms of roll pressure specifically with higher percentage of Alcell lignin. Therefore, addition of lignin would improve the process in terms of limitation and a vast range of process parameters can be used for the formulations containing lignin. In terms of the effect of process parameters on ribbon density, higher roll pressure results in higher ribbon density for all percentages of Alcell lignin. Nevertheless, the effect of screw speed on ribbon density is almost negligible. Increasing the screw speed while keeping the roll pressure constant, does not have considerable effect on ribbon density for formulations containing lignin. Given that the roll gap was variable in the experiments, increasing the screw speed increases the amount of powder pushed between the rolls, therefore, the gap between the rollers increases which corresponds to the increase of the ribbon thickness. Now, increasing the ribbon thickness decreases the stress applied on the powder as the force will be distributed over wider thickness of powder. However, this phenomenon is not envisaged to be significant compared to the effect of roll force.

In order to understand the behaviour of various formulations during the roller compaction process, the Stability Index (SI) of different blends were measured by FT4 powder rheometer. The stability index of 1 is ideal and implying that the material does not change during the characterisation. An appropriate explanation is provided in the Appendix about the stability index. The SI of the blends, containing 5%, 10% and 20% lignin were 0.729, 0.752, and 0.840 respectively. It implies that by increasing the lignin content in the blends, the stability of the powder blends increases. Moreover, the contours graphs show the higher stability for the blends with higher lignin percentage. On the other hands, the stability index was measured for the lactose blends as well. The SI of 5%, 10% and 20% lactose were 0.891, 0.714 and 0.587 respectively. These results illustrate that increasing the lactose percentage, leads to decrease in the blend stability.

For better understanding, the effect of formulations and materials on quality attributes of roll compaction process, flowability and cohesion for different materials used in this work were measured by FT4 powder rheometer and represented in Fig. 5.

It is observed that Alcell lignin has a better flowability (Flow Function = 6.38, easy flow) than lactose (FF = 3.54, poor flow). The methods and equations used for measuring powder flowability are described in Appendix A. On the other hand, lactose has greater cohesion (1.27 kPa) than Alcell lignin (0.611 kPa) and MCC (0.384). To analyse the effect of particle size and shape on the properties of materials, PSD and SEM characterisations were carried out. Fig. 6 presents the particle size distribution and SEM of the three used excipients. Image A and PSD of lactose show a wide range of particle size, which results in poor flow behaviour. Image C and PSD of Alcell lignin illustrates a wide range of particle size, similar to lactose, but with lower cohesion which causes easy flow. On the other side, image B and PSD of MCC 102 demonstrates a narrow particle size distribution, which leads to free flow behaviour. As it is demonstrated in the particle size graph, lactose and lignin have almost similar particle size (D50 = 37 μm), but MCC 102 has larger particles with a narrower range of particle sizes with more uniformity and higher flowability. In addition, Fig. 7 indicates the results of compressibility of the excipients measured by FT4 powder rheometer via compressibility test. Compressibility is a useful indicator of powder flowability, if it is cohesive or free flowing [39, 40].

As seen in Fig. 7, lactose shows the highest compressibility among all excipients, while MCC 102 has the lowest compressibility. The reason to use lactose/lignin as excipient is to improve the compaction behaviour of MCC 102 in the manufacturing process. Also, it is seen that lignin can be used to improve the compressibility of MCC 102 during the RC process.

The process map indicates that higher compressibility leads to a wide range of process parameters for different formulations containing lactose. However, lactose is cohesive material and poor flowing, and introducing lignin can improve the flow behaviour of formulation. A wide range of screw speeds for the blends with different percentages of lactose are shown in Fig. 3 [29–31]. For the lignin, low range of screw speed can be applied during the process (see Fig. 4). It means that at higher screw speed, more powders are pushed between the rolls and increasing screw speed would result in blockage due to less

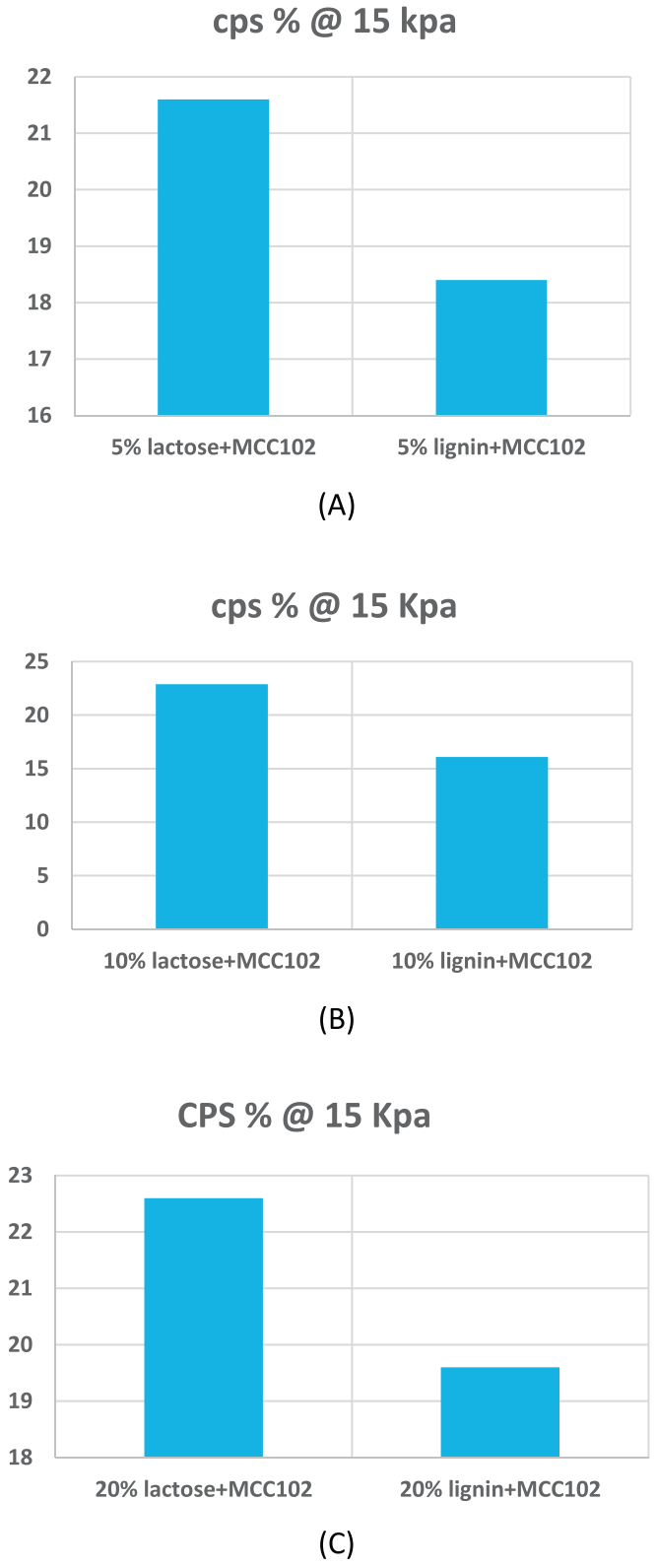


Fig. 8. Graphs of compressibility (CPS) of different blends measured by FT4 powder rheometer.

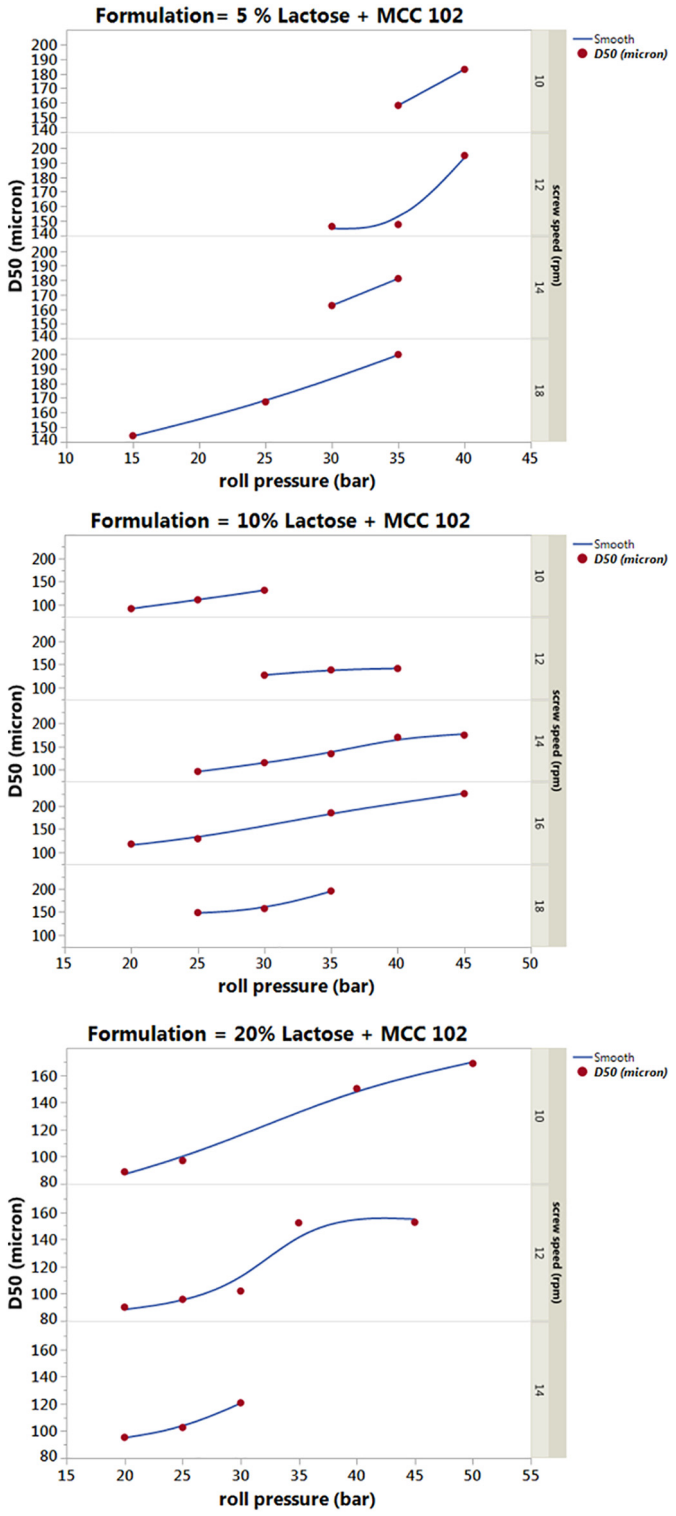


Fig. 9. Effect of process parameters on D50 of granules for lactose formulations.

compressibility of lignin compared to lactose. On the other hand, higher screw speed works better with more compressible materials like lactose. Comparing the cohesion of lignin and MCC, lignin has higher cohesion, and increasing the percentage of lignin would result in less process limitations. The higher ribbon density for formulations containing lignin as observed in Fig. 4, can be attributed to the affinity and interaction between lignin and MCC 102 as both materials are of cellulosic nature.

Physical properties of powders have an important influence on the quality attributes of products. We have to investigate the physical properties of materials and the behaviour of them as a component in the formulations. There is a relationship between particle size of powders as an inherent properties and their surface area. Materials with smaller particles have larger surface area, which cause them to be more compressible than the material with larger size. Therefore, lactose with

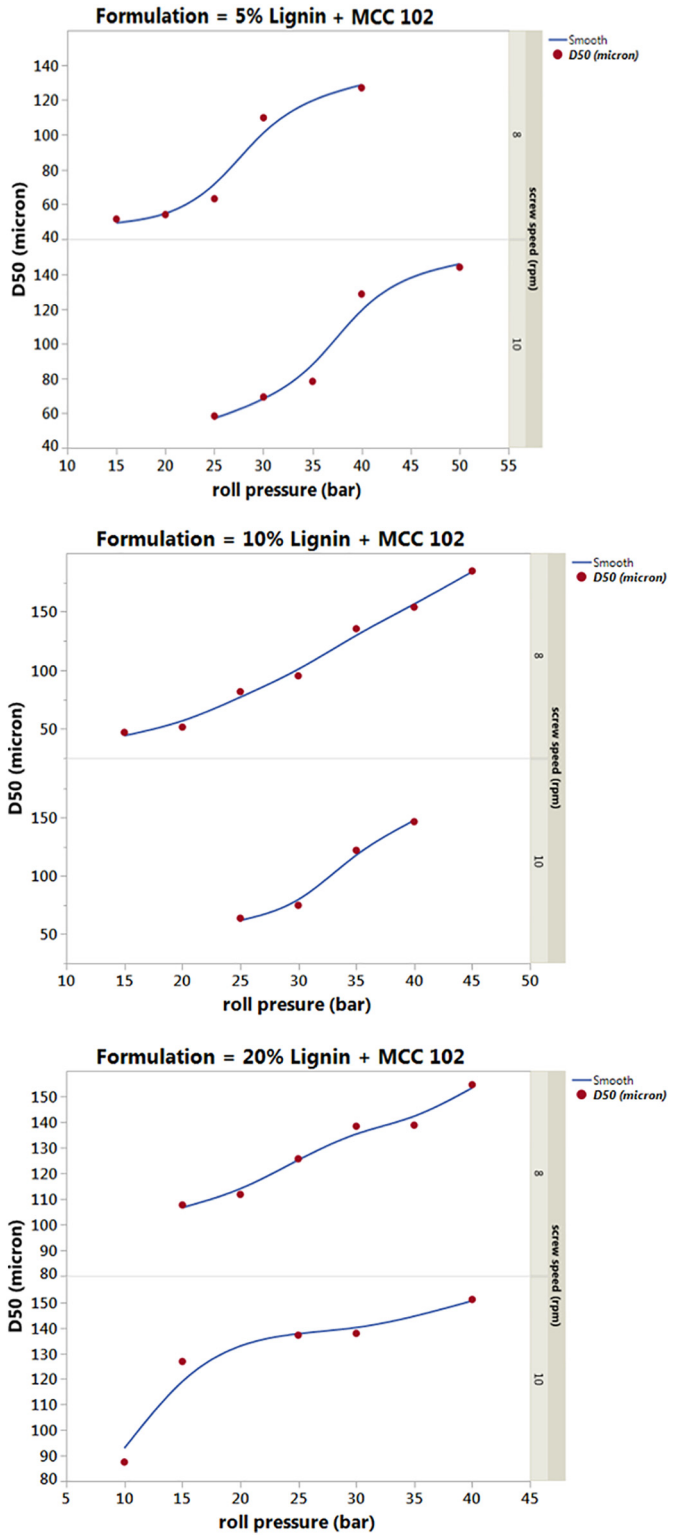


Fig. 10. Effect of process parameters on D50 of granules for Alcell lignin formulations.

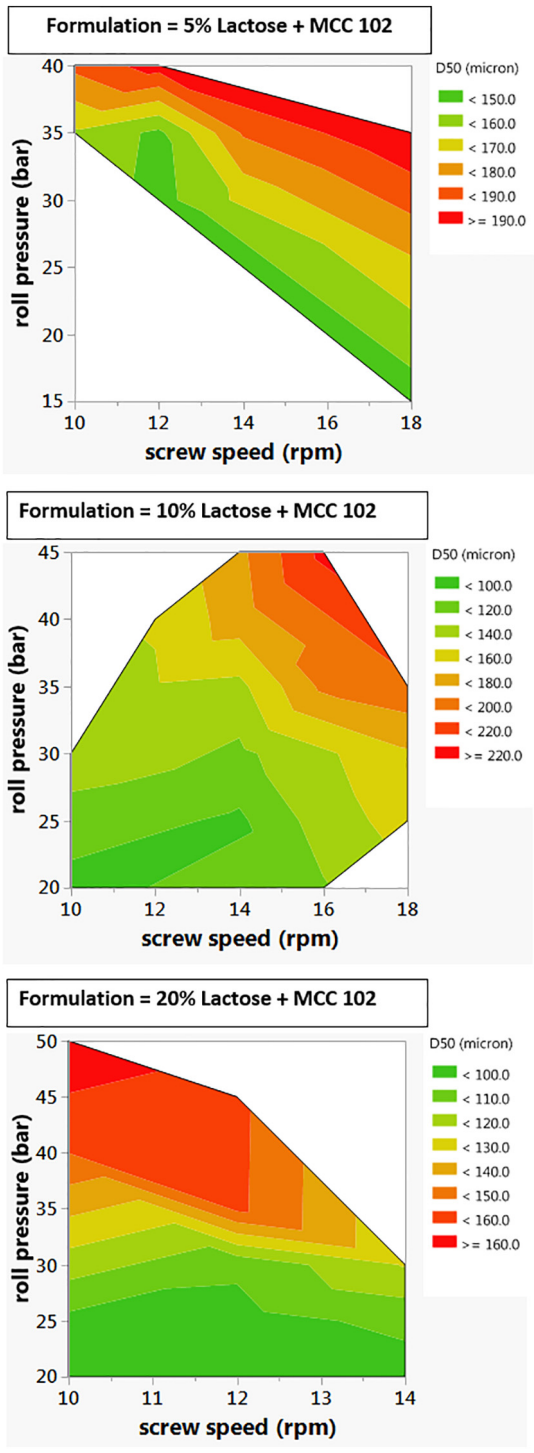


Fig. 11. Contour plot for d50 of granules (microns), formulation = 5, 10 and 20 wt% lactose.

smaller particle size indicates increased particle-particle contact which tends to be more compressible compared to MCC 102. For lactose, by increasing applied stress the compressibility increases due to smaller size which results in more efficient inter-particle packing.

To further understand the effect of blends properties on quality attributes of products, the results of different blends characterisation by FT4 powder rheometer are demonstrated in Fig. 8. The results confirm that blends with differing lactose percentages have higher compressibility than the blends with differing Alcell lignin percentages. For example, as shown in the Fig. 8A, due to the highest percentage of cohesion of lactose, the blends with lactose are more compressible.

3.3. Effect of process parameters on D50 of granules

Another critical quality attribute for dry granulation using roll compaction is granule size, as the tablet properties are dependent on the granule size. The produced ribbons were then milled to obtain the desired granules. For this section, D50 of granules was used as

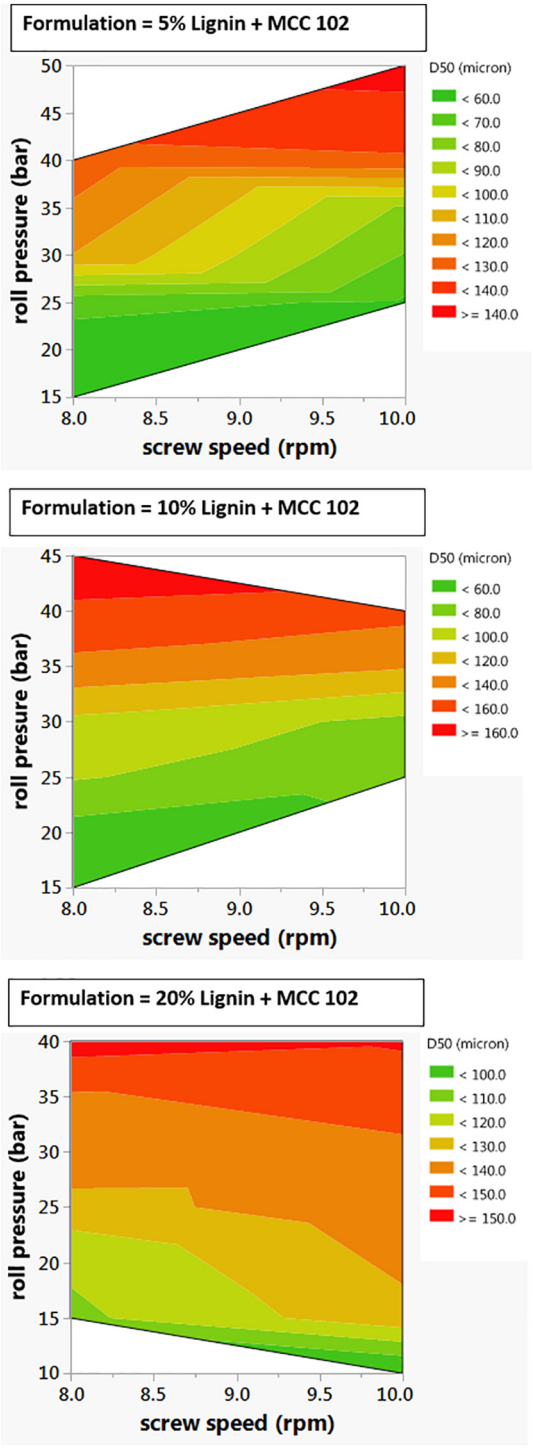


Fig. 12. Contour plot for d50 of granules (microns), formulation = 5, 10 and 20 wt% Alcell lignin.

representative granule size. The effect of process parameters on D50 of granules for different formulations are illustrated in Figs. 9 and 10. These maps are plotted by using *JMP 12 pro* software for D50 of granules versus roll pressure and screw speed. Fig. 9 illustrates the correlation between process parameters and D50 of granules for 5, 10 and 20 percentages of lactose. For each formulation, higher roll pressure leads to greater D50 at constant screw speed. As discussed, because of smaller particle size of lactose compared to MCC 102, the blends containing lactose are more compactible. Increasing the lactose percentage leads to denser ribbons, and consequently results in larger granules because

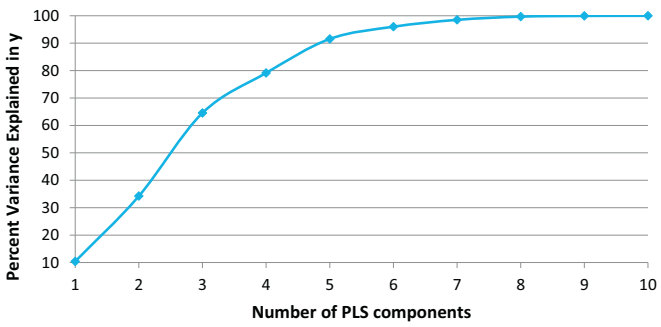


Fig. 13. Percent of density variance explained versus number of PLS components.

more shear force is needed to break up the ribbons in the mill for granule formation. In addition, it is seen that the effect of screw speed on D50 at constant roll pressure is almost negligible. Moreover, in the highest percentage of lactose (20%), due to inherent properties of lactose such as cohesion, a narrow range of screw speed and a wide range of roll pressure are observed. Due to higher cohesion of lactose than MCC 102, in the higher percentage of lactose, there are more limitations. In Fig. 10, the correlation between process parameters and D50 of granules for 5, 10 and 20 percentages of Alcell lignin are shown. These maps present a narrow range of screw speed and a wide range of roll pressure for these formulations. Because of Alcell lignin properties including less compressible and less cohesion, smaller D50 of granules were observed for formulations containing lignin. On the other hand, for different formulations of Alcell lignin, increasing the percentage of lignin leads to larger D50 of granules because of smaller particle size of lignin than MCC 102, higher compressibility and higher cohesion of lignin.

3.4. Effect of formulation on D50 of granules

The contours of D50 of granules versus roll pressure and screw speed are designed for different formulations of lactose and Alcell lignin, as shown in Figs. 11 and 12. These maps describe the limitations of process parameters and equipment as discussed before. The generation of uncontrolled fines is a common problem in dry granulation process. During milling process to produce granules, the particles, which are ≤125 μm, are known as fines [41]. In addition, the area in the process map with particle size smaller than 125 μm for each formulation reveals the amount of fines produced which should typically be avoided.

Fig. 12 indicates the correlation between process parameters and D50 of granules for different percentages of Alcell lignin. The same trend was observed for formulation with Alcell lignin. Higher percentages of Alcell lignin leads to larger particle size of granules and less percentage of fines. As discussed before, the compressibility of different blends with lactose are higher than Alcell lignin. It is concluded that, higher compressibility of lactose formulations leads to produce denser

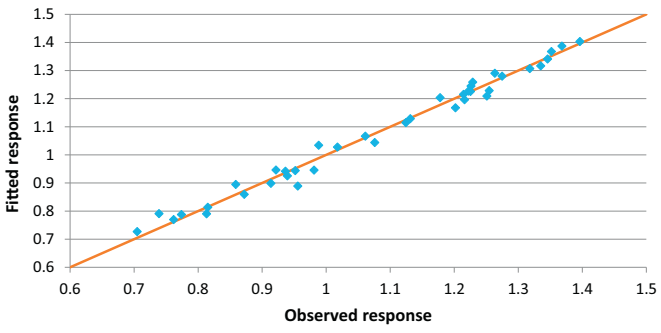


Fig. 14. Predicted versus measured ribbon density calculated by NIR.

and stronger ribbons, then, larger granule size. Less percentage of fines and bigger granule size are observed with 20 wt% of Alcell lignin compared to lower lignin content. Also, as seen, higher roll pressure leads to greater D50, while as mentioned before, screw speed does not have any serious effect on D50.

These plots, Figs. 11 and 12, also show that the amount of fines (particles ≤125 μm) are dependent on the roll pressure, increasing the roll pressure leads to denser powders, and larger granule size, result in a reduction in the amount of fines. At a constant roll pressure, increasing the screw speed results in enhancement of the particle size of granules for 5 and 10 wt% of lactose formulation. However, for 20% of lactose, the screw speed does not have any important influence on particle size of granules, in addition, the map shows more stability. By increasing the roll pressure, the influence on particle size of granules is more prominent.

4. NIR spectroscopy

NIR spectroscopy was conducted to correlate the obtained spectra to the ribbon density obtained by roller compaction. The aim is to evaluate the applicability of NIR as a process analytical tool (PAT) for development of continuous pharmaceutical manufacturing. The NIR spectroscopy has the ability to be used as on-line measurement tool of critical quality attributes of granules and ribbons such as density [21, 22, 24]. In order to evaluate the applicability of NIR for characterisation of various formulations and formulations containing lignin, the produced ribbons were characterised by a NIR probe to measure the envelope density. Off-line NIR spectroscopy was used by Multieye NIR instrument with the wavelength range of 1500–2200 nm and one probe to monitoring of Critical Quality Attributes. The NIR absorbance was found to be proportional to the envelope density of the ribbons. Partial Least Square (PLS) regression analysis was used for the calibration of the NIR results [22]. Cross validation analysis was conducted to calculate the numbers of principal components and the optimum number of components was obtained to be seven as shown in Fig. 13. Utilising seven PLS components show >98% variance in ribbon density. However, considering higher PLS components may cause over-prediction, which is a major problem in estimation of ribbon density. Once the model has been built and calibrated, it can be used to measure the envelope density using the NIR spectra as inputs. The PLS regression results are shown in Fig. 14 where it can be concluded that the built PLS model is capable of calibrating the NIR spectrum to the density of the ribbons with an R-squared of 0.98 as shown in Fig. 14.

5. Conclusions

The main objective of this study was to implement the quality-by-design approach to identify the correlation between critical process parameters (CPPs) and critical quality attributes (CQAs) of outputs from a dry granulation by roller compaction process. A variety of excipients with differing formulations were prepared and used in roll compaction process to produce ribbons and granules. Microcrystalline cellulose (MCC 102) was used as the base excipient, as it is a common widely used material in dry granulation process due to its inherent properties such as good compressibility because of fibrous structure and high capacity. Other formulations containing lactose and Alcell lignin were considered to understand the influence of formulation on the CQAs.

The effects of CPPs including roll pressure and screw speed on the CQA, including ribbon density as well as D50 were investigated. The results indicated that a variation in roll pressure has a considerable effect on ribbon density and granules size (D50) in the roller compaction process. At higher roll pressure and constant screw speed, the amount of powder between rolls are constant and more pressure leads to more densification of powder, especially for smaller particle size, cohesive and compressible powders, and results in a higher density and larger D50 of granules size. On the other hand, it was found that screw speed does not have any significant effect on critical quality attributes of products, and it affects other process variables such as the amount of powders, roll gap, and residence time of powders between rolls.

It was revealed that the properties and percentages of different excipients constrain the operability of the parameters used in roller compaction. However, as the process map is dependent on the formulation and equipment, generalisation of these process maps are needed based on dimensionless variables. The differences in mechanical properties of excipients leads to some differences in compaction behaviour during RC. Lactose shows higher compressibility than MCC 102 and Lignin. Therefore, lactose with smaller particle size, and larger surface area with increased particle contact tends to be more compressible than MCC 102, and can be used as modifier in the RC process. Also, lignin indicated almost similar behaviour with lactose, and can be a promising excipient in tablet manufacturing.

Another important objective of this study was to investigate the capability of Alcell lignin as natural polymer to use as excipient to improve powder properties, costs and delivery of tablets as final products. Alcell lignin, as a natural polymer can improve granulation process because of good flowability, low cost and ease of availability. Interestingly, it was revealed that less operational limitations was observed when lignin was introduced as an excipient in the formulations. Moreover, the applicability of NIR spectroscopy as PAT tool for on-line measurement of ribbon density in roller compaction process was investigated and NIR has been shown to be robust and reliable enough to be used as an on-line measurement in the RC process for formulations containing lignin.

Acknowledgements

This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750.

Appendix A. Appendix

A.1. Flow function

To measure the flowability of powders used in this study, the most commonly used parameter is flow function (FF) which is defined as [42, 43]:

$$FF = MPS/UYS \quad (A.1)$$

where MPS refers to the major principle stress acting on the powder, and UYS denotes the unconfined yield strength of the powder at the MPS. The values for MPS and UYS can be measured by shear cell test using FT4. The powders are categorised based on the FF values as listed in Table A.1.

Table A.1
Classification of powders based on FF values.

Type of flow	Flow function (FF)
Free flowing	FF > 10
Easy flowing	4 < FF < 10
Cohesive	2 < FF < 4
Very cohesive and non flowing	FF < 2

A.2. Compressibility

Compressibility is a measure of how density changes as a function of applied normal stress. Indeed, compressibility is the ability of powder to reduce in volume by applying stress. For powders, the bulk property is influenced by many factors such as particle size distribution, cohesivity, particle shape, and particle surface texture. The standard measurement method for compressibility of powders utilises a vented piston to

compress the sample under increasing normal stress, and the compressibility is calculated using the following equation:

$$\text{Compressibility} = \text{percentage change in volume after compression } (\%) \quad (A.2)$$

As we mentioned in the manuscript, the compressibility was measured by FT4 powder rheometer. For powders, density is a function of applied normal stress. The changes in density of powders as a function of applied normal stress are known as compressibility [44]:

$$\text{Bulk Density} = \frac{\text{Split Mass}}{\text{Volume after Compression}} \quad \left(\frac{\text{gr}}{\text{mL}}\right) \quad (A.3)$$

$$\text{Compressibility Index} = \frac{\text{Density after Compression}}{\text{Conditioned Bulk Density}} \quad (A.4)$$

The compressibility of powders can be measured by using of Carr's index and Hausner Ratio [45]:

$$\text{Compressiblity or Carr's Index Formula} = 100 * \frac{(V0 - Vfinal)}{V0} \quad (A.5)$$

$$\text{Hauner's ration} = \frac{V0}{V} \quad (A.6)$$

The range of normal stress was between 1 and 2–4–6–8–10–12–15 kPa.

The Basic Flowability Energy (BFE) value were measured by FT4 powder rheometer for the materials and the results showed that MCC 102 has the highest value of BFE = 177 (MJ), this value indicates that this material is free-flowing. On the other hand, BFE of lactose was the lowest BFE = 81.1 mj, it means lactose is more cohesive than other materials and for Alcell lignin BFE = 119 mj.

A.3. Stability index

Stability index is a simple analysis carried out to understand whether the formulation being analysed changes during the analysis. It is an indication of the stability of formulation during characterisation. The stability test runs the formulation through a series of identical measurements, and similar results would be obtained if the formulation being tested is stable. If the stability index is approximately 1, it means the powder is physically stable. The SI > 1 or SI < 1 shows unstable powder. FT4 powder analyser uses the following stability index formula [46, 47]:

$$\text{Stability Index, SI} = \text{Energy Test 7}/\text{Energy Test 1} \quad (A.7)$$

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International Journal of Biological Macromolecules 124 (2019) 354–359

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: http://www.elsevier.com/locate/ijbiomac

Effect of lignin on the release rate of acetylsalicylic acid tablets

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ARTICLE INFO

Article history:
Received 27 June 2018
Received in revised form 5 November 2018
Accepted 14 November 2018
Available online 15 November 2018

Keywords:
Lignin
Dry granulation
Roll compaction
Drug dissolution
Drug release
Hydrolysation
Acetylsalicylic acid

ABSTRACT

The main focus of this paper is on the improvement of formulations utilising non-conventional bio-based excipients to improve tablet release rates. Two different formulations were considered. The first formulation contains Alcell lignin, lactose monohydrate and microcrystalline cellulose as excipients and acetylsalicylic acid (aspirin) as active pharmaceutical ingredient (API). The second formulation contains lactose monohydrate and microcrystalline cellulose as excipients and aspirin as API. The prepared formulations were roller compacted followed by milling, sieving, and tableting. The tablets were then characterised in terms of dissolution rate in order to compare the release rates. Results indicated that tablets containing Alcell lignin have quicker release, faster disintegration times and higher tablet hardness for all samples with differing process parameters. Higher API dissolution has been attributed to the amorphous structure of lignin and its interaction with aspirin, which increases dissolution of the API.

1. Introduction

Three different methods are considered for tablet manufacturing in the pharmaceutical industry, i.e. direct compaction, dry, and wet granulation. Recently, there has been focus on direct compaction due to cost and time effectiveness as less number of processing steps are involved. Moreover, the tablets produced by direct compaction have faster dissolution rates [1]. However, in order to improve powder flowability and bulk density, especially for poor flowing materials, granulation has proved useful. Dry granulation is continuous and is the preferred method for moisture and heat sensitive materials as no binder is used [2–6].

Today, one of the major challenges facing the pharmaceutical industry is to enhance the bioavailability which plays a crucial role in drug development [7]. Tablet release rate has a significant effect on tablet bioavailability [8] in which higher release rates result in higher bioavailability and lower side effects. Currently, the most common method for enhancing the bioavailability of drugs is preparation of amorphous solid dispersion. In an amorphous solid dispersion (ASD), the API is transformed to amorphous phase from crystalline by various techniques, and then API is dispersed in a polymeric carrier, which enhances the dissolution of API molecules.

Excipients are inert substances used in drug production to assist manufacturing and control the dosage, quality, stability, bioavailability, toxicity and efficacy [9–11]. For example, sugar compounds such as lactose and cellulose derivatives such as MCC are the most commonly used excipients in tablet manufacturing [10,12,13]. In order to investigate drug release, healing rates, disintegration and dissolution tests have been extensively studied [14–19]. Several researchers have illustrated that the influence of excipients on release of oral dosage drugs is significant [20]. The type of excipient, its physical and chemical properties, and interaction with API can effect processability and stability of tablets as well as overcome the drug side effects [21]. Therefore, tablet formulation can be considered as a critical factor in pharmaceutical production due to its considerable effect on disintegration, dissolution and drug release rate [7,20,22–24].

Various researchers have focused on improved tablet release rate and drug absorption, etc. by developing novel excipients. Due to some issues in relation to side effects and release rates of solid dosage forms [25], use of materials with desired functionality as excipient in tablets are increasing. In tablet manufacturing, amorphous materials are showing great promise as excipients as they exhibit higher dissolution compared to crystalline equivalents due to disordered structure and higher free energy [25–29]. On the other hand, the thermodynamic instability of amorphous excipients used in tablets, might result in relaxation and crystal growth of crystalline API molecules over time which is not favourable for bioavailability [30].

Recently, biological macromolecules have attracted attention for use as excipient in tablet production to enhance drug dissolution and

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https://doi.org/10.1016/j.ijbiomac.2018.11.136
0141-8130/

bioavailability. A number of studies have been carried out on lignin to improve chemical modification [31–33], and to develop new pharmaceutical formulations with increased functionality [34,35] because of lignin structure which contains phenolic and aliphatic hydroxyl groups [35]. Lignin has a high potential to be used in tablet manufacturing either with chemical modification or without chemical modification [32]. Furthermore, some researchers have investigated the ability of lignin's nanoparticles (NPs) in drug delivery due to its non-toxicity, biodegradability and stability. Lignin has also been used to transport hydrophobic drugs [35]. Lignin is an amorphous polymer and non-amphiphilic in nature, and displays high chemical stability due to 3D network structure [36]. As lignin is rich in phenolic and aliphatic hydroxyl groups [32], it interacts with most API molecules through π-π stacking and hydrogen bonding, and this makes lignin potentially useful as a drug carrier to enhance bioavailability [16,17,21,26,28,34,36,37–41].

Aspirin, which is known as a delayed-release drug is utilised as a model API in this work [42]. In fact, the dissolution rate of aspirin is the rate-limiting step, which controls the absorption and bioavailability. Moreover, another challenge associated with aspirin is that it hydrolyses to salicylic acid upon exposure to aqueous solutions, which should be taken into account during the dissolution tests [8,15,38,42–44]. Wang et al. have investigated aspirin hydrolysis during dissolution tests, and found out that the hydrolysis of aspirin occurs during dissolution [44]. Sumirtapura et al. studied the dissolution of different types of acetylsalicylic acid products, and distinguished time lags for differing aspirin tablets [43]. Peltonen et al. utilised three different tablets containing aspirin for dissolution tests. The first type of tablets contained aspirin and MCC; the second ones consisted of aspirin and lactose, while the third ones included aspirin, lactose and MCC. They investigated the effect of pH on aspirin release rate and found higher release at higher pH. Moreover, they reported that adding lactose to aspirin in the formulation leads to increased release rate. On the other hand, adding MCC results in decreased release rate [15].

In comparison with other literature, the authors have tried to analyse the dissolution of different formulations containing aspirin as API and various excipients. Lignin was used as a new excipient to evaluate its performance in tablet manufacturing in order to improve drug release rates. Indeed, the purpose of this study is to investigate the effect of Alcell lignin on tablet properties including hardness, disintegration time and drug release rate. The main aim is to explore the possibility of using lignin to enhance bioavailability of poorly water-soluble drugs. Two different formulations are utilised, one formulation containing Alcell lignin and another one without lignin. First, two different blends are roller compacted to produce ribbons. Then, the produced ribbons are milled to make granules. Afterwards, these granules are used to produce tablets. Different tablet characterisation tests including; disintegration, hardness and dissolution tests are carried out to understand the effect of lignin on drug release rates.

2. Experimental procedure

2.1. Materials and methods

In order to prepare the formulations, acetylsalicylic acid (Alfa Aesar, 99% $C_9H_8O_4$) was utilised as a model API. Different excipients were utilised including microcrystalline cellulose (MCC SANAQ® 102 L USP/NF/EP), lactose monohydrate (Lennox USP, NF, BP, Ph, pure pharma grade) and Alcell lignin (Tecnaro (Ilsfeld, Germany)). More details on the lignin used in this study can be found elsewhere [33]. To prepare the mixtures, 1% w/w magnesium stearate (Sigma-Aldrich, Ph. Eur., BP, ≥90% stearic and palmitic acid basis), as lubricant and croscarmellose sodium (CCS) (IMCD NF, PH. Eur., JP) as disintegrant were used in the formulations. Table 1 illustrates the two different formulations considered; in the first one; 5 wt% of aspirin was mixed with 20 wt% of lactose, 20 wt% of lignin, 3 wt% of CCS and 1 wt% MgSt, and the rest is MCC 102. The second formulation was prepared with 5 wt% of aspirin, 20 wt% of lactose, 3 wt% of CCS, 1 wt% MgSt, and the rest is MCC 102. All components were mixed using a Morphy Richards Stand Mixer. Orthophosphoric acid (analytical reagent grade, Fisher Scientific UK) and acetonitrile, HPLC grade, 99.7 + % min Liquid (Alfa Aesar) were mixed to prepare mobile phase for HPLC analysis.

Table 1
Characteristics of different formulations used in this study.

Material	A	B
Acetylsalicylic acid (wt%)	5	5
Alcell lignin (wt%)	20	0
Lactose (wt%)	20	20
MCC 102 (wt%)	51	71
Croscarmellose sodium (wt%)	3	3
Magnesium stearate (wt%)	1	1

2.2. Equipment and instruments

2.2.1. Dry granulation by roll compaction and milling process

To prepare the tablets, the dry granulation method was used for the entirety of this work in a series of ribbon production, milling, and tabletting. The ribbons were produced using a roller compactor (Freund TF-MINI) integrated with a vertical screw feeder for feeding the formulations. The rollers dimensions are 100 mm in diameter and 25 mm in width. The considered process parameters included screw speed (SS) and roll pressure (RP), while roll speed was kept constant at 4 rpm. The screw speed was changed between 10 and 14 rpm, and roll pressure was changed between 30 and 50 bars in the ribbon production experiments. The density of produced ribbons was measured using GeoPyc density analyser (Micrometrics Instrument Corp., Norcross – USA). The produced ribbons were then milled using a conical mill (Laboratory Comil 193 AS) with mesh size of 813 μm, and impeller speed of 3000 rpm. The particle size distribution (PSD) of fine powder and granules were measured using Microtrac S3500 particle size analyser.

2.2.2. Tablet preparation and characterisation

A benchtop single punch tablet press (Gamlen Tableting GTD-1 D series) was used to produce the tablets with different formulations. 100 mg of two different formulations of produced granules were pressed to make tablets in a 6 mm (diameter) die. The tablet compression was carried out at 180 mm/min speed under fixed load of 400 kg. Croscarmellose sodium was used as super disintegrant in tablet preparation experiments [23].

Hardness of the produced tablets was measured using a tablet hardness tester (Pharma Test PTB311E). To measure the disintegration time, Pharma Test PTZ-DIST- Disintegration Test Instrument (Hainburg, Germany) was used. The apparatus chamber was filled with 900 mL of deionized water and the apparatus paddle was adjusted at 100 rpm. Three samples were tested in deionized water at 37 °C for each process parameters and for two different formulations. All the disintegration tests were conducted until the tablets completely disintegrate. The dissolution of produced tablets was performed using a Pharma Test PTWS 120D 6-Station Tablet Dissolution Testing Instrument (Hainburg, Germany).

The concentration of the API in each sample was measured using High Performance Liquid Chromatography (HPLC). Chromatography was performed using an Agilent (Agilent Technologies, Waldbronn, Germany) 1260 Infinity II HPLC system. The HPLC system consisted of a quaternary pump G1311B, a diode array detector G1315D set at wavelengths of 200 nm for acetylsalicylic acid and salicylic acid, autosampler G1329 B and a thermostated column compartment G1316A set at 25 °C. The system operated under isocratic flow at 0.75 mL/min using mobile phases consisting of A) 0.1% Ortho-phosphoric acid; B) acetonitrile; A/B = 50/50, v/v. The injection volume was 10 mL. The total run time was 10 min, and the type of column used was Kromasil 5C18 (250 × 4.6 mm).

2.3. Dissolution test procedure

The dissolution chamber was filled with 500 mL of prepared medium 0.1 N HCl (ACS, ISO, Reag. Ph Eur, Hydrochloric acid fuming 37 wt%) at pH = 1.2. The medium temperature was kept constant at 37 ± 0.5 °C and the stirrer was adjusted to a speed of 75 rpm [42]. When the temperature reached 37 °C, one tablet was placed in each dissolution vessel to run the dissolution test for 120 min. Three millilitres of the dissolution medium were withdrawn at 5, 10, 20, 30, 40, 50, 60 and 120 min, then medium was replaced with the same amount, immediately. Then, the samples were filtered using Captiva Econofilters (PTFE membrane, 13 mm diameter, 0.2-μm pore size) syringes to prepare for the analysis by HPLC at 200 nm wavelength, immediately, due to hydrolysis of acetylsalicylic acid.

In order to prepare the buffer solution (pH = 1.2) for the dissolution tests, 2 g sodium chloride was dissolved in 200 mL deionized water. Then, it was diluted with deionized water in a 1000 mL volumetric flask and 7 mL HCl was added. In order to prepare the calibration solutions for HPLC analysis, 5 mg of acetylsalicylic acid and 5 mg salicylic acid were dissolved in 20 mL of buffer solution, separately. Then, they were mixed to prepare the calibration solution. Afterwards, the prepared solutions were diluted with buffer solution 6 times. The standard curves of drug concentration vs peak area were drawn for different formulations giving $R^2 = 0.99$.

3. Results and discussion

3.1. Dissolution profiles for two different formulations

Two different formulations were evaluated to find the effect of Alcell lignin on the aspirin tablet release rate. One formulation contains Alcell lignin, MCC 102 and lactose as excipients and the other one contains lactose and MCC 102 as excipients. Both formulations contain aspirin as API. Fig. 1 illustrates the graphs of drug release rate for tablets prepared at various process parameters. As seen, different levels of screw speed and roll pressure were considered in this study. Interestingly, the results show that the tablets containing Alcell lignin have higher release rate than the tablets without lignin for all prepared samples. In addition, the equilibrium dissolution for the tablets containing lignin is greater which is attributed to the enhancement of solubility of ASA with addition of lignin. It is also seen that faster release kinetics is obtained for the tablets containing lignin such that the majority of the API are

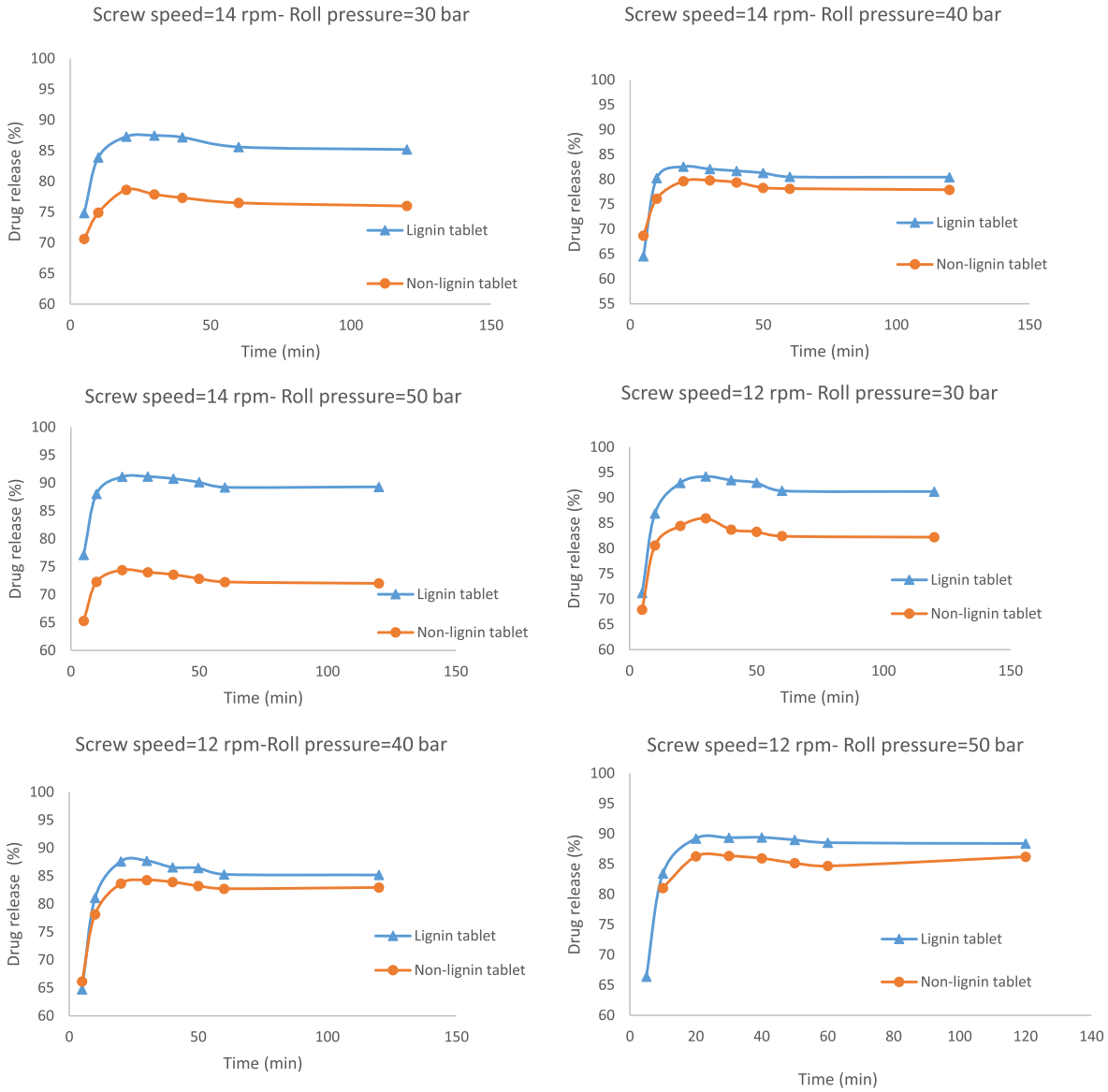

Fig. 1. Dissolution release rate of acetylsalicylic acid for different lignin and non-lignin tablets at different process parameters.

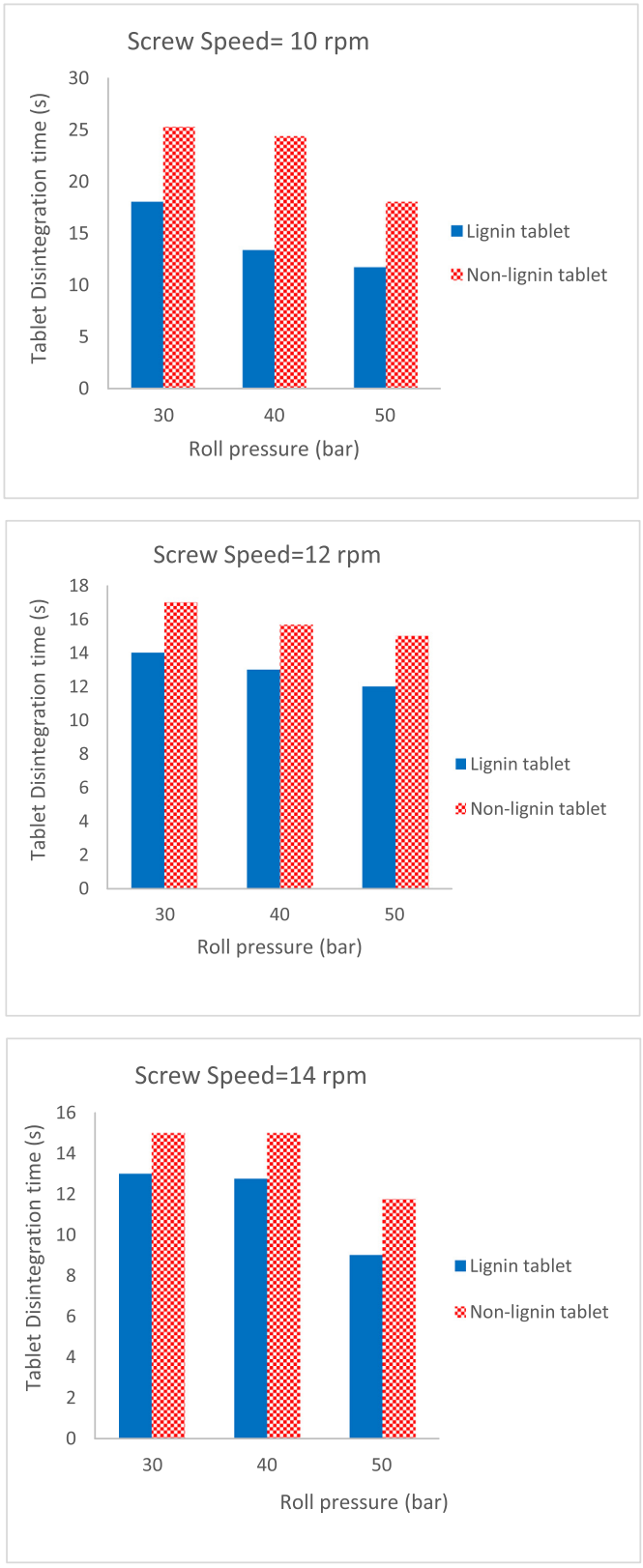

Fig. 2. Disintegration time of tablets prepared with and without lignin as function of process parameters.

dissolved in the first 10 min of the dissolution test. Moreover, the tablets prepared with lignin indicated less variability in the dissolution measurements. The data is provided in the Supplementary file for both formulations.

In other words, tablets containing lignin with very high release rate acts as a disintegrating agent in the dissolution chamber, facilitate the dissolution kinetics, and accelerate to equilibrium release. Moreover, due to amorphous nature of lignin, it may be concluded that lignin enhances the solubility of API due to its disordered structure and higher Gibbs free energy of the amorphous phase in the dissolution media. The cross-linked structure of lignin is likely to have an effect on dissolution and disintegration as well. Peltonen et al. [15] studied the effect of pH on the release rate of aspirin tablets with different formulations (B (aspirin & lactose), A (aspirin, lactose &MCC) and C (aspirin &MCC)). They illustrated in pH 1.2 the release rate of aspirin with the different formulations are low and it does not show 100% release rate after >200 min. Maximum release rates of the formulation B was around 90% after 200 min. For formulation A, the release rate was around 80% after 500 min and for formulation C was around 70% after 500 min.

The roll compaction process parameters affect the release rate of aspirin also in which the effect of roll pressure is more significant compared to screw speed. For the tablets without lignin, increasing roll pressure (at constant screw speed of 14 rpm) results in reduction of API dissolution, which could be attributed to the particle size of granules, which produce the tablets. In the roll compaction process, increasing the roll pressure results in enhancement of granule size. However, the effect of process parameters on the API dissolution is not significant, because the dissolution depends mainly on the chemical structure of API and interaction with the dissolution medium. In fact, the granulation improves the flowability of particles in the manufacturing.

3.2. Effect of process parameters on tablet disintegration time

The effect of roll pressure and screw speed as the main process parameters of dry granulation on the tablet disintegration time for the two formulations is shown in Fig. 2. In terms of the effect of roll pressure as process parameter on disintegration time of tablets, the results illustrate that increasing the roll pressure while keeping the screw speed constant, results in decreasing the disintegration time for both formulations. Increasing the roll pressure results in higher densify of ribbons during the roll compaction process, and subsequently produce larger granules because higher mechanical energy is required to break up the ribbons during the milling step. The tablets made with larger granules will be more porous, and subsequently leads to faster disintegration time. It is also observed from Fig. 2 that the tablets containing lignin have faster disintegration time than non-lignin tablets due to the amorphous and inherent structure of lignin, which has higher affinity towards the solution media compared to MCC and lactose.

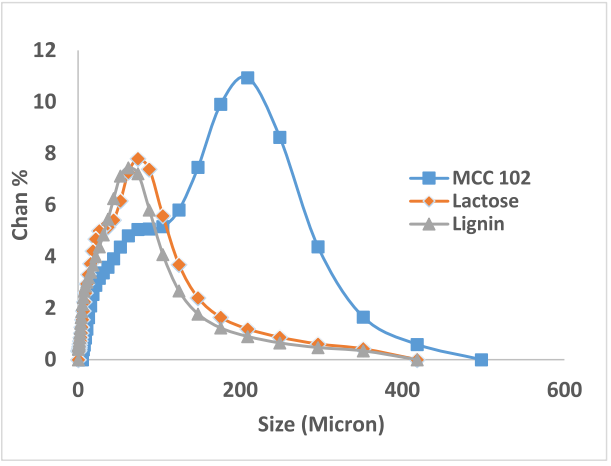

Fig. 3. Particle size distribution of materials; MCC 102, lactose and lignin.

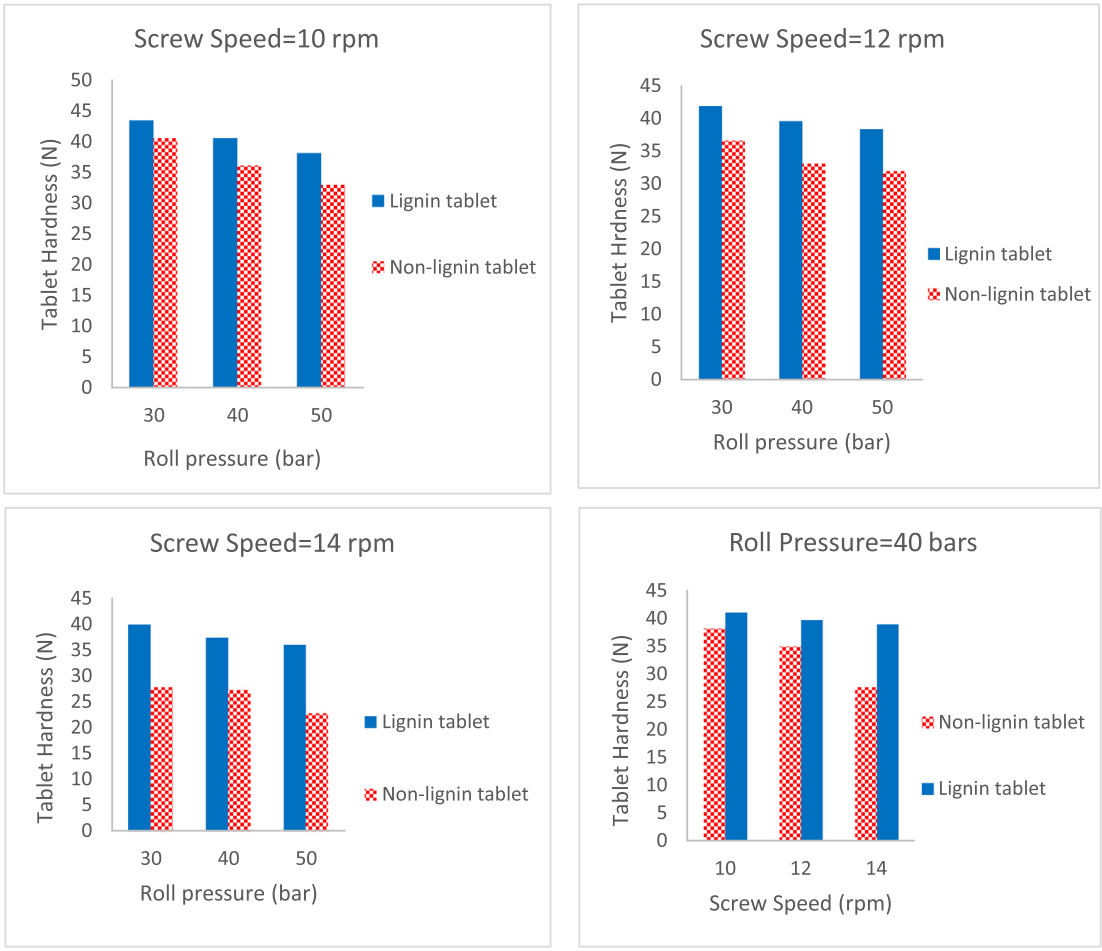

Fig. 4. Hardness of tablets prepared with and without lignin as function of process parameters.

Moreover, the particle size of raw materials used as excipients is shown in Fig. 3. As observed, lignin has smaller particle size compared to MCC 102, and introducing lignin as an excipient results in better compaction behaviour. In fact, smaller particles provide better particle-particle contact during the roll compaction and denser ribbons are produced, which in turn results in larger granules in the milling stage [45]. Furthermore, the size distributions of the used granules for tableting are shown in the Supplementary file. It is seen that the formulation containing lignin has slightly larger granule size, which results in faster disintegration time.

3.3. *Effect of process parameters on tablet hardness*

Fig. 4 illustrates the hardness of the tablets prepared using the two formulations as a function of process parameters. The results reveal that the lignin tablets have higher hardness than non-lignin tablets for all samples. Also, it can be seen that increasing the roll pressure leads to reduction of tablet hardness due to larger granules being obtained at higher roll pressure which in turn leads to weak physical bonds between particles. The results also indicate that by increasing screw speed, the tablet hardness decreases; however, the change is not considerable. In addition, the standard range of tablet hardness is between 39 and 79 N, therefore the lignin tablets are within the standard range of hardness. The reason why tablets containing lignin display higher hardness can be attributed to the interaction between lignin and other constituents of the formulation where lignin acts as a binder thereby increasing tablet hardness.

4. Conclusions

The main aim of this study was to investigate the effect of lignin-based excipients on release of aspirin tablets. Its influence on release rate and tablet properties at varying processing conditions were assessed. Results illustrate that lignin tablets, compared to non-lignin tablets, have higher hardness, faster disintegration time, and higher release rate. Indeed, the critical quality attributes of the tablets were improved by introducing the lignin. Higher release rate of tablets with lignin formulation are are attributed to the amorphous structure of lignin and its interaction with the API, which presumably improves drug solubility and therefore bioavailability, key factors in oral dosage development. On the other hand, higher roll pressure leads to more densified ribbons associated with lignin blends and consequently, larger granules are produced. These larger granules result in porous tablets, which lead to faster disintegration times as solute diffuses faster into the tablets. Also, the greater hardness for the tablets containing lignin are attributed to better affinity between lignin and MCC which leads to lignin acting as a tablet binder.

Acknowledgements

This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750.

The authors also would like to thank Dr. Ali Sheikhi, Department of Mathematics, University of Limerick, for his useful comments on the statistical analysis.

Appendix A. Supplementary data

The results pertaining to granule size distribution as well as variability of the dissolution tests and *t*-test results can be found in the Supplementary file online at www.sciencedirect.com. A paired-samples *t*-test was performed to assess the difference between release rate of two different types of tablets, without lignin and with lignin. Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijbiomac.2018.11.136.

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Cellulose (2019) 26:6165–6178
https://doi.org/10.1007/s10570-019-02522-w

ORIGINAL RESEARCH

Application of lignin in controlled release: development of predictive model based on artificial neural network for API release

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Received: 27 March 2019 / Accepted: 19 May 2019 / Published online: 25 May 2019

Abstract Predictive models for simulation of drug release from tablets containing lignin as excipient were developed in this work. Two predictive models including Artificial Neural Network (ANN) and hybrid ANN-Kriging were developed to simulate the tablet dissolution. Measured data was collected on the release rate of aspirin tablets prepared by dry granulation via roll compaction followed by milling and tableting. Two formulations were considered, one with lignin and one without. The main aim is to show the effect of lignin as a bio-based natural polymer in tablet manufacturing to control drug dissolution. For the ANN model development, process and formulation parameters including roll pressure and lignin content were considered as the input, while API dissolution was considered as response. The predictions were compared with measured data to calibrate and validate the model. To improve the predictability of the model, Kriging interpolation was used to enhance the number of training points for the ANN. The interpolated data was trained and validated. The final concentration and the dissolution rate were predicted by ANN as well as ANN-Kriging models, and the R^2 of greater than 0.99 for most cases was obtained. The validated model was used to evaluate the effect of process parameters on the release rate and it was indicated that the tablets containing lignin have higher release rate compared to tablets without. Also, it was revealed that process parameters do not have significant effect on the tablet release rate, and the tablet release rate is mainly affected by the lignin content. The results indicated that ANN-based model is a powerful tool to predict the API release rate for tablets containing various formulations, and can be used as a predictive tool for design of controlled release systems.

Keywords ANN model · Kriging interpolation · Controlled release · Lignin · Pharmaceuticals · Tableting · Dry granulation

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Introduction

Most drugs are administered in solid phase, such as crystalline particles which are processed into tablets or

capsules by adding excipients (Siepmann and Siepmann 2013). In pharmaceutical manufacturing of solid-dosage oral formulations, there are different unit operations such as blending, granulation, drying, tableting, and coating among which granulation is the key processing step as the tablet properties depend on the granules attributes such as size, API content, porosity, etc. (Hansuld and Briens 2014; Shirazian et al. 2018; Suresh et al. 2017; Vervaet and Remon 2005). In granulation processes, pharmaceutical granules are formed from fine powder (e.g. excipient and API) using various methods such as roller compaction, high-shear wet granulation, twin-screw granulation, fluidised bed granulation, and hot melt extrusion (Asada et al. 2018; Hansuld and Briens 2014; Ko et al. 2018; Passerini et al. 2010; Walker et al. 2007). The main reason for granulation is to improve the powder flowability as well as tablet properties. Among various granulation processes developed so far, dry granulation is a suitable process for moisture and heat sensitive formulations, as no binder is used in the process. Dry granulation is usually carried out using roller compaction process in which the formulation is first compacted to produce ribbons, and then granules are produced by milling the ribbons. The critical process parameters in roller compaction process include roll pressure, roll speed, roll gap, and screw feeder speed (Al-Asady et al. 2015; Omar et al. 2016).

Understanding the relationship between process parameters of the roll compaction process and tablet properties is of great importance for development of pharmaceutical manufacturing and implementing Quality-by-Design (QbD) approach. The effect of process parameters and material properties on critical quality attributes of ribbons and granules have been reported in literature. Both experimental (Khorasani et al. 2015, 2016) and theoretical studies (Loreti et al. 2017; Pérez Gago et al. 2016; Reynolds et al. 2010; Souihi et al. 2015) have been conducted to understand the roller compaction process. In terms of modelling studies, Johanson has proven to be a robust and rigorous mechanistic model for better understanding of roller compaction process (Reynolds et al. 2010). Although, previous studies reveal the correlation between critical process parameters and granules/ribbons properties in roller compactor processes (Pishnamazi et al. 2019a), understanding the relationship between process parameters and tablet dissolution still remains a challenge and opportunities arise in helping to improve tablet dissolution rate by tuning formulation and process parameters.

Drug dissolution is an important quality attribute of pharmaceutical tablets in which the kinetics and equilibrium concentration (solubility) of Active Pharmaceutical Ingredient (API) release from the tablets is of utmost importance (Siepmann and Siepmann 2013). The main focus of controlled release systems is to manipulate the release rate of APIs through different techniques such as incorporating into polymeric matrix (Castro-Dominguez et al. 2017), and loading drug in stimuli-responsive nanocarriers (Fleige et al. 2012), and therefore enhancing bioavailability for poorly water soluble APIs. Nowadays, a big challenge facing the pharma industry is poor solubility of newly produced drugs in the body, i.e. bioavailability. According to Biopharmaceutics Classification System, BCS Class II and BCS Class IV many drugs are of poor solubility and bioavailability (Daousani and Macheras 2016). It has been recognised that seven out of ten of drugs never reach the patients. Development of solid dispersions have been reported to be effective in improving the solubility of BCS Class II drugs (Van den Mooter 2012). Amorphous solid dispersions provide high dissolution rates because of their disordered structure and higher Gibbs free energy compared to crystalline APIs (Ziaee et al. 2017).

Recently, lignin has attracted much attention as it may be used to improve the release of bio-active compounds (Chowdhury 2014; Collins et al. 2019). Lignin is a cross-linked natural polymer, cheap, and available (Culebras et al. 2018). Due to amorphous nature of lignin which has higher free energy, it can be used as modifier to enhance the bioavailability of poorly soluble APIs. However, understanding the effect of lignin on dry granulation using roller compactor, and finding a correlation between lignin content and tablet dissolution rate remains a big challenge. Developing a robust predictive model for designing controlled release systems based on natural polymers is of great importance for pharmaceutical industry.

Therefore, there is a definite need for a comprehensive study to correlate the critical process parameters of roller compactor as well as formulation with tablet dissolution as the key critical quality attribute. A powerful tool is the development of a process model where inputs and outputs can be correlated. Different models have been used for pharmaceutical

manufacture such as mechanistic models (Sajjia et al. 2017; Shirazian et al. 2018) and soft computing approaches (Mustafa et al. 2017; Shirazian et al. 2017). Artificial Neural Network (ANN) is a soft computing method which is capable of predicting the process and making correlation between process inputs and outputs (Ismail et al., 2019a, b). Applicability, robustness, and reliability of ANN in pharmaceuticals have been verified in the literature (Das and Chakraborty 2016; Mustafa et al. 2017; Shirazian et al. 2017).

The main objective of the current study is the development of a comprehensive ANN-based model for prediction of dissolution rate of tablets prepared by roller compaction followed by milling and tableting. In order to enhance the bioavailability of API, lignin is used as excipient and the tablet dissolution rate is measured for tablets containing lignin and without lignin. Aspirin is used as model API in this study.

Experiments

Materials and methods

Two different formulations containing API and excipients were considered in this study for preparation of tablets. The excipients used include microcrystalline cellulose (MCC 102, SANAQ®), lactose monohydrate (Lennox USP, NF, BP, Ph, pure pharma grade), and Alcell lignin (Tecnaro, Germany). More details on the lignin used in this study can be found elsewhere (Culebras et al. 2018). Acetylsalicylic acid (Alfa Aesar, 99% $C_9H_8O_4$) was utilised as API in both formulations. Magnesium stearate (Sigma-Aldrich, Ph. Eur., BP, $\geq$ 90%) was used as lubricant for the compaction experiments, and Croscarmellose sodium (CCS) (IMCD NF, PH.Eur., JP) was used as disintegrant in both formulations. The percentage of the materials used in two different formulations are listed in Table 1. To prepare the mixture, all the materials were blended using a Morphy Richards Stand Mixer. HCl acid (ACS, ISO, Reag. Ph Eur, Hydrochloric acid fuming 37%) was used for preparation of buffer solutions for dissolution tests. For preparation of the mobile phase for analysing the API concentration with HPLC, Ortho-phosphoric acid (analytical reagent grade, Fisher Scientific UK) and acetonitrile, HPLC grade, 99.7 + % min Liquid (Alfa Aesar) were mixed together.

Table 1 Different formulations used in this work

Material (% w/w)	Formulation 1	Formulation 2
Acetylsalicylic acid	5	5
Alcell lignin	20	0
Lactose	20	20
MCC 102	51	71
Croscarmellose sodium	3	3
Magnesium stearate	1	1

Equipment and instruments

Dry granulation method was utilised to produce the tablets for two different formulations. In order to do dry granulation process, roller compaction was carried out. The roller compactor, ("Freund TF-MINI"), with roll diameter of 100 mm and width of 25 mm integrated with a vertical screw feeder was used to produce ribbons. The roll pressure was changed between 30 and 50 bar in the experiments. A conical mill (Laboratory Comil 193 AS) with a screen (mesh size of 813 μm) and impeller speed of 3000 rpm was used to produce the granules from the ribbons. The considered process parameters included screw speed (SS) and roll pressure (RP), while roll speed was kept constant at 4 rpm. The screw speed was changed between 10 and 14 rpm, and roll pressure was changed between 30 and 50 bars in the ribbon production experiments.

For tableting process, a single punch tablet press (Gamlen Tableting GTD-1 D series) was applied. For preparation of each tablet, 100 mg of granules of each formulations were measured and compacted to produce tablets in a 6 mm die. The tablet compression was carried out at 180 mm/min speed under fixed load of 400 kg.

Dissolution procedure

For the dissolution analysis, buffer solution at pH = 1.2, including 0.1 N HCl (ACS, ISO, Reag. Ph Eur, Hydrochloric acid fuming 37% wt.) was prepared as dissolution medium. 500 ml of the dissolution test chamber was filled with the buffer solution, with the

constant temperature at 37 ± 0.5 °C and 75 rpm stirrer speed. The experiment was run for 120 min, and the samples (Three mL) were withdrawn from the dissolution chamber at 5, 10, 20, 30, 40, 50, 60, 120 min. Afterward, the samples were filtered and the concentration of API was measured using HPLC at wavelength of 200 nm. The dissolution tests were carried out in triplicate, and the average values were used for modeling.

High-Performance Liquid Chromatography (HPLC) was used to measure the API concentration in each samples via an Agilent (Agilent Technologies, Waldbronn, Germany) 1260 Infinity II HPLC system. The HPLC setup consisted of a quaternary pump G1311B, a diode array detector G1315D set at wavelengths of 200 nm for acetylsalicylic acid, auto-sampler G1329 B and a thermostated column compartment G1316A set at temperature of 25 °C. The system operated under isocratic flow at 0.75 mL/min using mobile phases consisting of A) 0.1% Ortho-phosphoric acid; B) acetonitrile; A/B = 50/50, v/v. The injection volume was 10 mL. The total run time was 10 min, and the type of column used was Kromasil 5C18 (250 × 4.6 mm) (Pishnamazi et al. 2019b).

Model development

ANN structure

In order to develop a predictive model, artificial neural network (ANN) approach was used in which the process parameters and material properties are correlated with critical quality attributes. Roll pressure, screw speed, and lignin content in the formulation were considered as the inputs, whereas the kinetics and final API dissolution were considered as outputs for developing ANN. The preliminary results indicated that screw speed has negligible effects on the quality attributes of ribbons, therefore, screw speed was omitted from the process parameters. An ANN model consisting of two hidden layers was developed as shown in Fig. 1. *JMP Pro 14* software was used for developing the ANN model and analysing the results.

To find the optimum ANN structure, different transfer functions were tested, and the best results were obtained for the structure consisting of 6 non-liner (hyperbolic tangent), 2 liners, and 2 Gaussian functions in the first layer; with 6 non-linear nodes for the second layer (see Fig. 1). In ANN modelling using *JMP*, the linear combination of input variables (roll pressure and lignin content) are not transformed when using the linear activation function, while for the non-linear function, the hyperbolic tangent term is used as follows (SAS_Institute 2016; Shirazian et al. 2017):

$$\frac{e^{2z}-1}{e^{2z}+1} \tag{1}$$

where z is a linear combination of input variables.

In order to build ANN model, 60% of the measured data was used to train the network, while 40% was used for model validation and testing the developed model in prediction of the API release rate. The network was trained to predict the concentration of API at different sampling time intervals, as function of lignin content and roll pressure of roller compactor. The developed ANN model was used for prediction of API release rate, in which the predictive behaviour and accuracy of the model is assessed by comparing the predicted values and the measured values. The coefficient of determination (R^2) which indicates the goodness of fitting is calculated as (Barrasso et al. 2015; Shirazian et al. 2017):

$$R^2 = 1 - \frac{\sum_i (f_i - y_i)^2}{\sum_i (\bar{y}_i - y_i)^2} \tag{2}$$

where f refers to the predicted points, and y refers to the observed values. i denotes the set of experimental run. Also, root-mean-squared error (*RMSE*) is calculated as:

$$\mathrm{RMSE} = \sqrt{\frac{\sum_i (f_i - y_i)^2}{n}} \tag{3}$$

where n denotes the number of measurements.

ANN-Kriging hybrid model

In order to improve the predictability of the developed ANN model for API dissolution, Kriging interpolation method was used to enhance the number of training and validating points for the ANN. Ordinary Kriging interpolation was developed based on two inputs and eight outputs which are the dissolution percentage at various times. Kriging method predicts a response y_k at an interpolated point x_k as a weighted sum of the

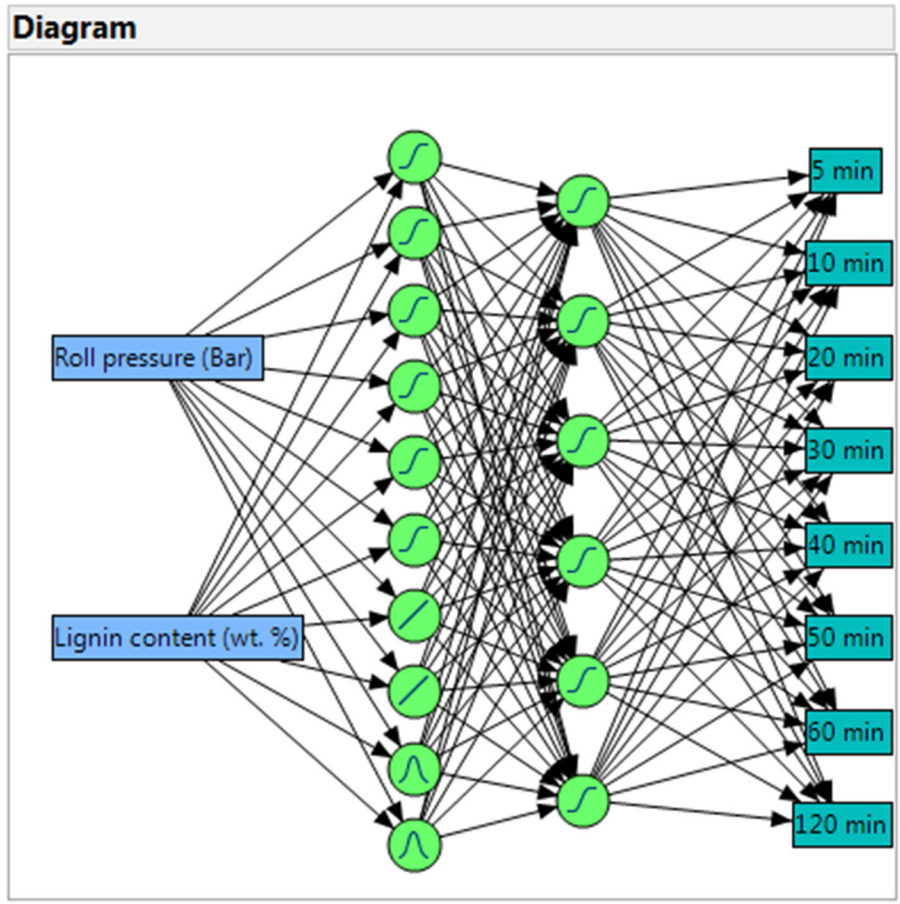

Fig. 1 Structure of developed ANN for prediction of drug release

observed responses (y_1, $y_2 \ldots y_n$) where x_k falls in the neighbourhood of their corresponding sampling points (x_1, x_2, $x_3 \ldots x_n$) (Boukouvala et al. 2011):

$$y_k = f(x_k) = \sum_{i=1}^{n} w_i f(x_i) \tag{4}$$

w_i is the weighted sum (kriging weights) which depends on the Euclidian distance h:

$$h = \left\| x_i - x_j \right\| \tag{5}$$

In Kriging algorithm, the main objective is to calculate the set of Kriging weights assigned to each group of n clustered points in the neighbourhood of x_k where the derived variogram model leads the sum of the weights to unity. In calculating the interpolated prediction $f(x_k)$ at x_k, the observed responses (y_1, $y_2 \ldots y_n$) for sampled points (x_1, x_2, $x_3 \ldots x_n$) that are in the neighbourhood and nearer to x_k will have more influence on predicting $f(x_k)$. Indeed, the higher number of neighbouring points and the nearer these neighbouring points are to x_k, $f(x_k)$ will be calculated with more confidence (Ismail et al., 2019a, b).

In ordinary kriging interpolation, the experimental variogram is calculated from the experimental data points to statistically quantify the dataset in a form that fits statistical equations (exponential, Gaussian, cubic…etc.). After fitting the experimental and theoretical variograms, kriging weights are then calculated to determine the interpolated response.

A two-dimensional kriging interpolation was conducted on the experimental data obtained from the dissolution experiments to predict the dissolution of API at new data points. The reliability and validity of the hybrid ANN-kriging has been proved in our previous works (Ismail et al., 2019a, b). Ordinary Kriging interpolation was performed in *Matlab* where the lignin content (%) and roller pressure (bar) were taken as input parameters and API dissolution at 5, 10, 20, 30, 40, 50, 60 and 120 min as output parameters.

Interpolation was conducted at 10 new points for each dimension in which 121 points were obtained after applying Kriging. The interpolated kriging data was used to improve the empirical ANN model prediction compared to using just experimental data.

The structure of the developed ANN-Kriging is shown in Fig. 2. As seen, the hybrid model contains two hidden layers, each layer constitutes of three nodes which makes the model simpler and faster to solve. Also, a combination of linear and nonlinear transfer functions has been used for the hybrid model to train the network for prediction of data.

Results and discussion

ANN model

The developed ANN model was first trained using the experimental data collected on the release rate of tablets containing aspirin. The trained network was then used to validate the model. The results of training and validation are listed in Table 2 for the concentration of API at different times, and the final concentration of API at the time of 120 min (final). As seen, the model is very well trained with the experimental data, and the R^2 of 1 is obtained for all points, while for the validation R^2 of 0.99 is obtained for most cases except for predicting the concentration of API after 5 min which could be attributed to high release rate at the beginning of the dissolution test. It is clearly observed that the model can predict the release rate of API with high accuracy, and can be used as a powerful predictive tool for the design of release systems based on lignin. However, it should be pointed out that there might be a risk of over-prediction in this system as small number of experimental points are used. Therefore, Kriging approach was used to train the network for more data points and prevent the risk of over-prediction.

ANN-Kriging model

The predicted release rate versus the measured values for both training and validation for the hybrid ANN-Kriging model are depicted in Fig. 3. Moreover, the statistical data of the calibration and validation for the hybrid ANN-Kriging is listed in Table 3. After Kriging, the number of data points are increased to 121 points to make a more robust predictive model.

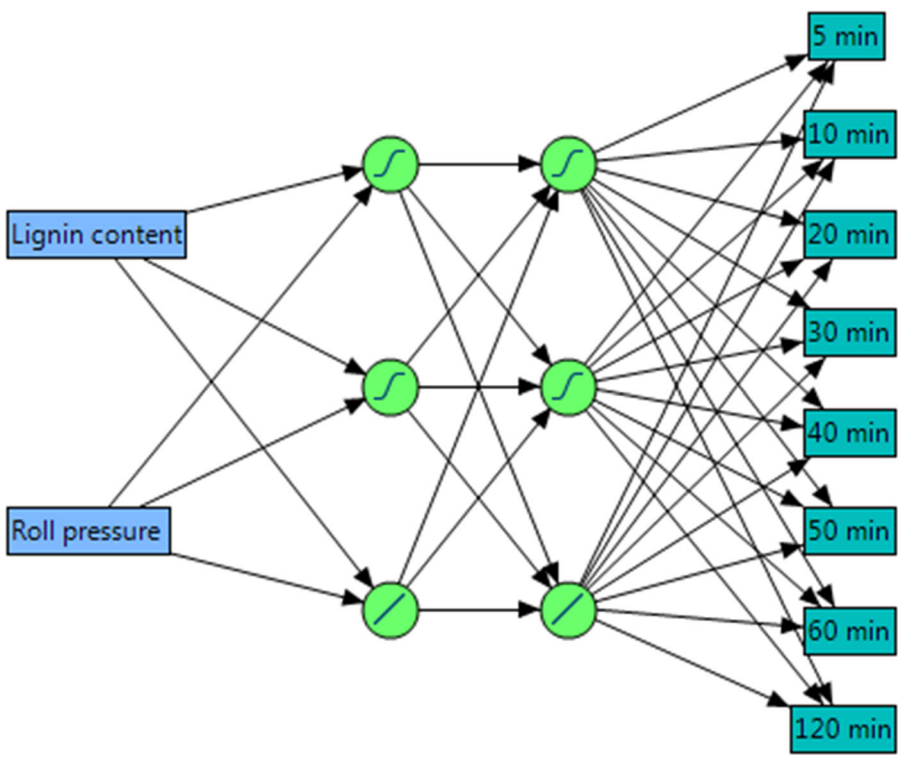

Fig. 2 Structure of developed ANN-Kriging hybrid model for prediction of drug release

Table 2 Statistical data of ANN calibration and validation

Times (min)	Data set	R^2	RMSE	Mean Abs Dev	−LogLikelihood	SSE	Data points
5	Training	1	8.7e−13	7.5e−13	− 105.4	3.0e−24	4
	Validation	0.52	2.6	1.9	4.8	14.0	2
10	Training	1	2.1e−13	1.8e−13	− 110.9	1.9e−25	4
	Validation	0.99	0.2	0.2	− 0.2	0.1	2
20	Training	1	3.7e−13	3.2e−13	− 108.8	5.6e−25	4
	Validation	0.99	0.5	0.4	1.5	0.5	2
30	Training	1	4.3e−13	3.7e−13	− 108.2	7.3e−25	4
	Validation	0.99	0.6	0.6	1.7	0.6	2
40	Training	1	4.3e−13	3.7e−13	− 108.2	7.5e−25	4
	Validation	0.99	0.4	0.4	1.1	0.4	2
50	Training	1	2.9e−13	2.4e−13	− 109.8	3.3e−25	4
	Validation	0.91	1.5	1.4	3.7	4.7	2
60	Training	1	4.1e−13	3.5e−13	− 108.4	6.7e−25	4
	Validation	0.99	0.1	0.1	− 0.9	0.04	2
120	Training	1	4.0e−13	3.3e−13	− 108.5	6.4e−25	4
	Validation	0.99	0.3	0.3	0.6	0.2	2

1/3 of the data points were used for validation, while 2/3 were used for training the network. It is clearly seen that the model is well trained for all the training points and the cross validation can confirm the model can be used for prediction of the dissolution. Also, similar to the ANN model, some deviations are observed for the dissolution data after 5 min, however R^2 has been significantly improved for 5 min data from 0.52 to 0.67 for the validation stage.

Simulation of the release rate using ANN model

The validated model was used to simulate the release rate of API for the tablets prepared with two formulations. The experimental and predicted release rates for the tablet without lignin, and the tablets containing lignin are represented in Figs. 4 and 5, respectively. The graphs of release rate indicate that the release rate is very high at the beginning of dissolution test, and more than 60% of the API is released after 5 min. After 20 min, the drug concentration in the solution reaches the highest values, and then decreases, and finally become plateau which is considered as the equilibrium point. The reason for reduction in the concentration of API after 20 min could be attributed to the dissociation of aspirin which undergoes hydrolysis during the dissolution test. Aspirin is partially hydrolysed to salicylic acid and acetyl salicylic acid upon exposure to aqueous solutions (Pishnamazi et al. 2019b).

It is also observed in Figs. 4 and 5 that the release rate of aspirin is higher in the tablets containing lignin such that higher dissolution rate is observed in the dissolution test of tablets containing lignin. This could be due to amorphous nature of lignin which enhances the dissolution of aspirin. It is observed that the model is robust and can predict the release rate and the final concentration as well.

Design space for the API release

The developed model was used to understand the effect of process parameters of roll compaction as well as formulation on the release rate of API. In roller compaction process, roll pressure is the most important parameter compared to other parameters such as screw speed and roll speed (Pishnamazi et al. 2019a). The effect of roll pressure and lignin content on the equilibrium concentration of API in the buffer solution is shown in Fig. 6. The roll pressure was considered between 30 and 50 bar, and the lignin content between 0 and 20 wt%. It is indicated that by increasing the lignin content in the formulation, the dissolution of API increases significantly which consequently can

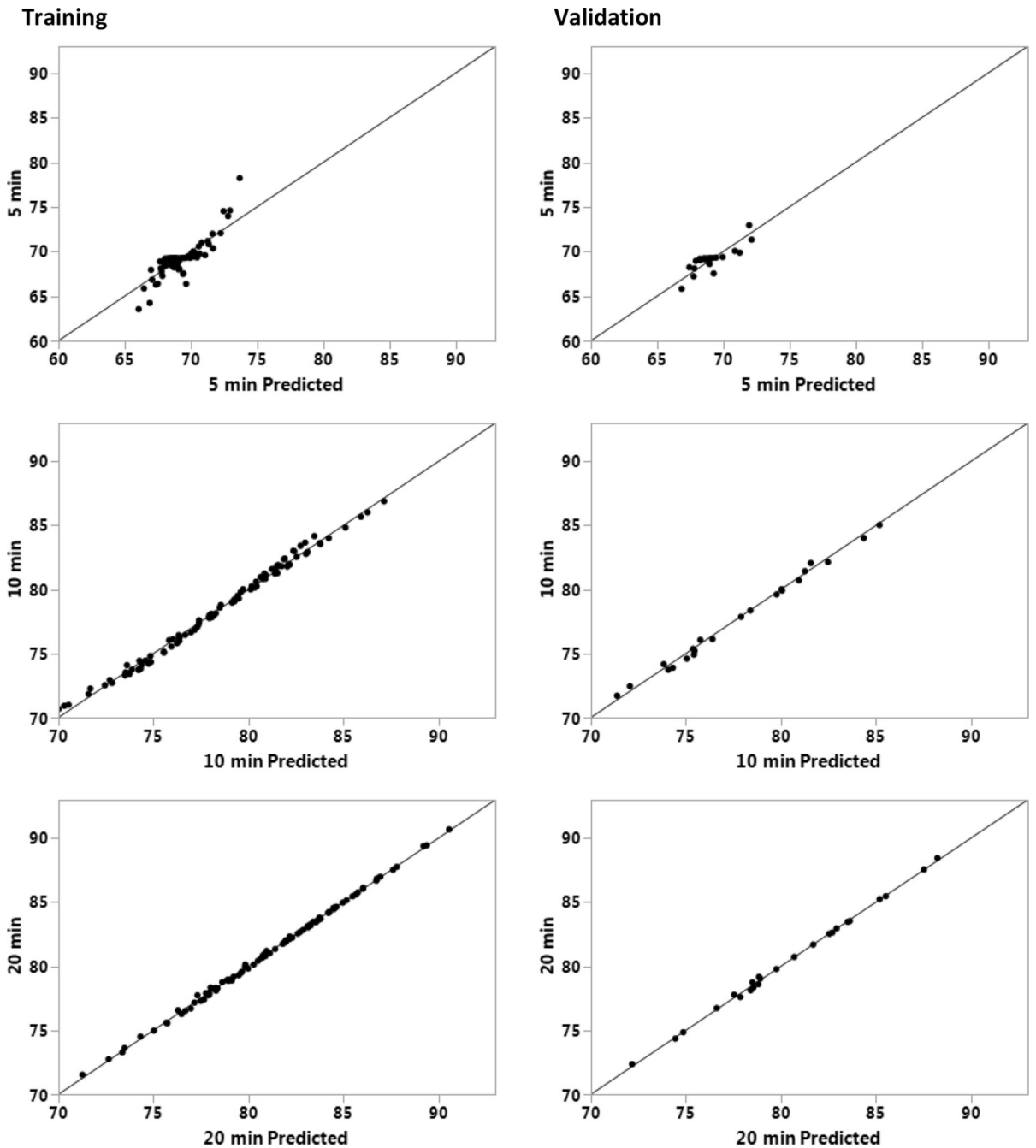

Fig. 3 Actual versus predicted values of drug release for the hybrid ANN-Kriging model

enhance the bioavailability of API. Also, it is seen that by increasing the pressure, the dissolution decreases, however the effect of roll pressure on the dissolution is not significant compared to the effect of lignin content because the dissolution of API is highly dependent on the chemistry of formulation and the dissolution medium. It is observed that increasing roll pressure decreases the equilibrium concentration of API which is attributed to the size of granules. As the roll pressure increases, denser ribbons are produced, which results in formation of larger granules in the milling step. Larger granules in the prepared tablets results in lower

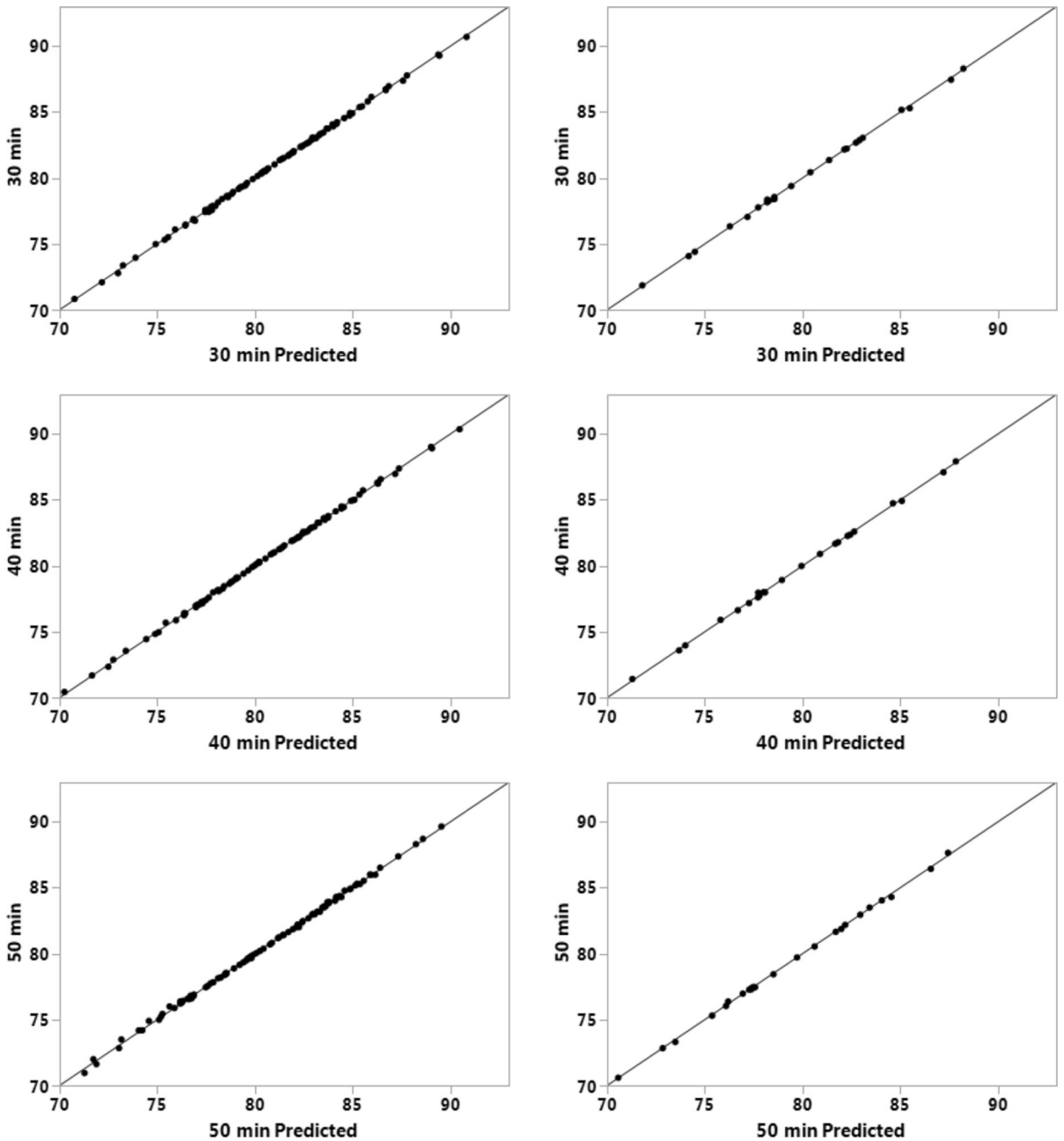

Fig. 3 continued

dissolution as the surface area of the granules decreases and reduce the surface energy and dissolution.

Conclusions

A new formulation containing lignin was designed in this work to enhance the bioavailability of drugs. The tablets were prepared using dry granulation method followed by milling and tableting. In order to design and predict the release rate of API, an artificial neural

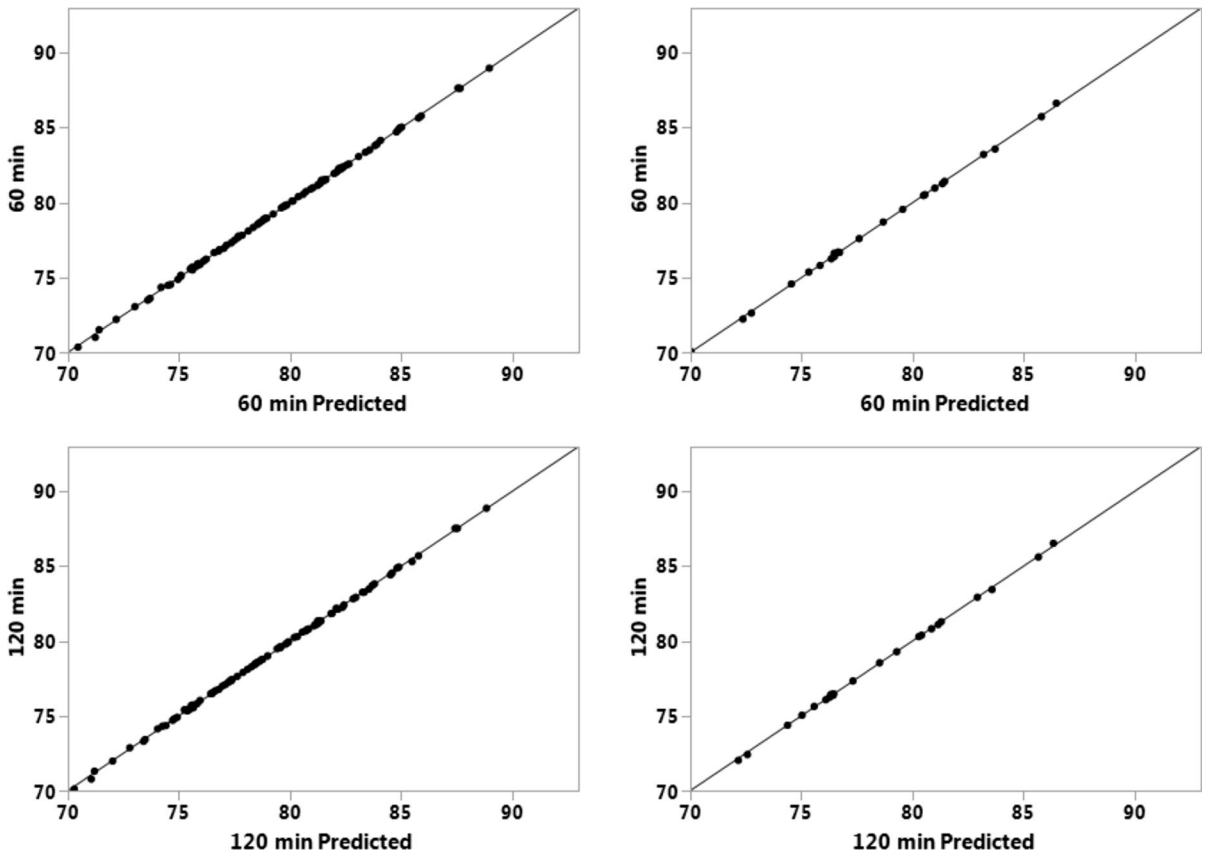

Fig. 3 continued

Table 3 Statistical data of hybrid ANN-Kriging calibration and validation

Times (min)	Data set	R^2	RMSE	Mean Abs Dev	−LogLikelihood	SSE	Data points
5	Training	0.69	0.98	0.68	135.83	93.45	97
	Validation	0.67	0.89	0.71	31.15	18.84	24
10	Training	0.99	0.34	0.27	32.50	11.10	97
	Validation	0.99	0.30	0.26	5.54	2.23	24
20	Training	0.99	0.13	0.09	− 60.92	1.62	97
	Validation	0.99	0.14	0.10	− 12.88	0.48	24
30	Training	0.99	0.07	0.05	− 113.76	0.54	97
	Validation	0.99	0.07	0.06	− 27.58	0.14	24
40	Training	0.99	0.07	0.057	− 116.05	0.52	97
	Validation	0.99	0.07	0.05	− 27.56	0.14	24
50	Training	0.99	0.10	0.07	− 83.30	1.02	97
	Validation	0.99	0.12	0.08	− 16.13	0.36	24
60	Training	0.99	0.06	0.05	− 133.06	0.36	97
	Validation	0.99	0.06	0.05	− 31.47	0.10	24
120	Training	0.99	0.07	0.05	− 120.85	0.47	97
	Validation	0.99	0.07	0.05	− 29.28	0.12	24

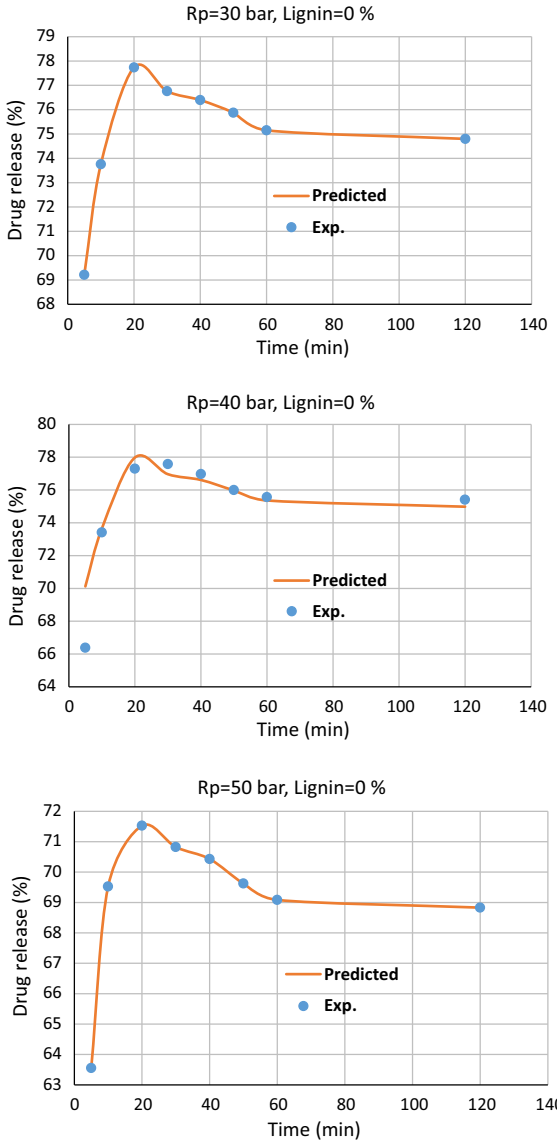

Fig. 4 Comparison between simulated and measured values of drug release. Tablets with no lignin. ANN model

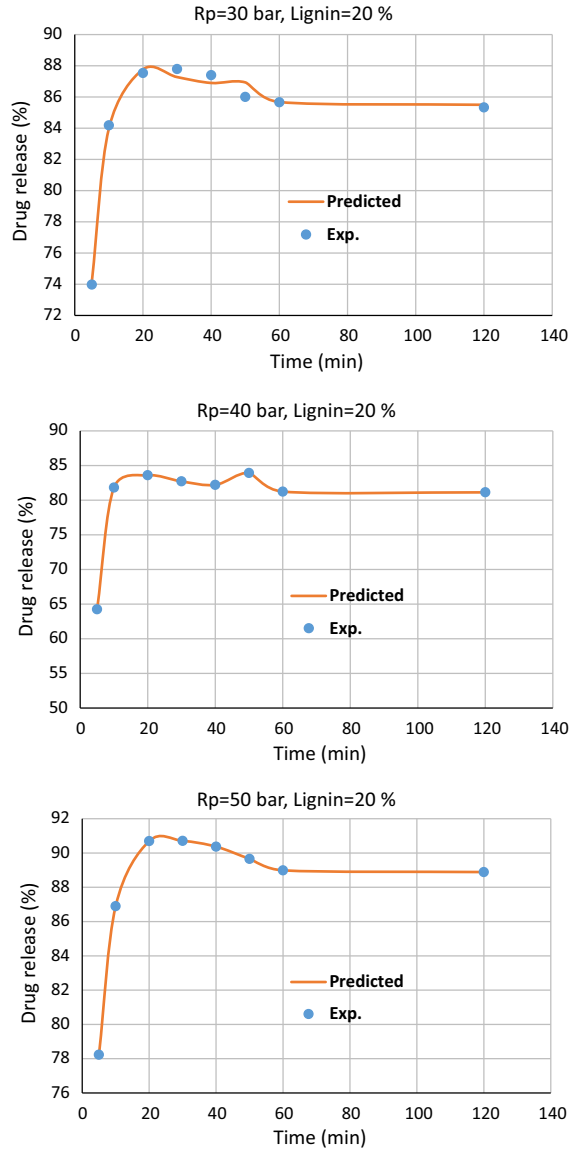

Fig. 5 Comparison between simulated and measured values of drug release. Tablets with lignin. ANN model

network (ANN) model was developed considering two hidden layers and combining various activation functions, i.e. linear, hyperbolic tangent, and Gaussian. The ANN model as well as hybrid ANN-Kriging were developed to predict the dissolution of the drug. Two formulations, one containing lignin, and the other one without lignin were considered to investigate the effect of lignin on the API release rate. The results of release rate indicated that the tablets containing lignin have higher release rates of API. The results of simulation revealed that the developed model can predict the release rate with high accuracy and R^2= 0.99 was obtained for most cases. The model was used to predict the kinetics and equilibrium of the release rate and great agreement was obtained between the predicted and measured data. The validated model was then used to understand the effect of process parameters on the release rate, and it was revealed that increasing roll pressure decreases the release rate, because larger granules are produced which in turn results in lower release rate.

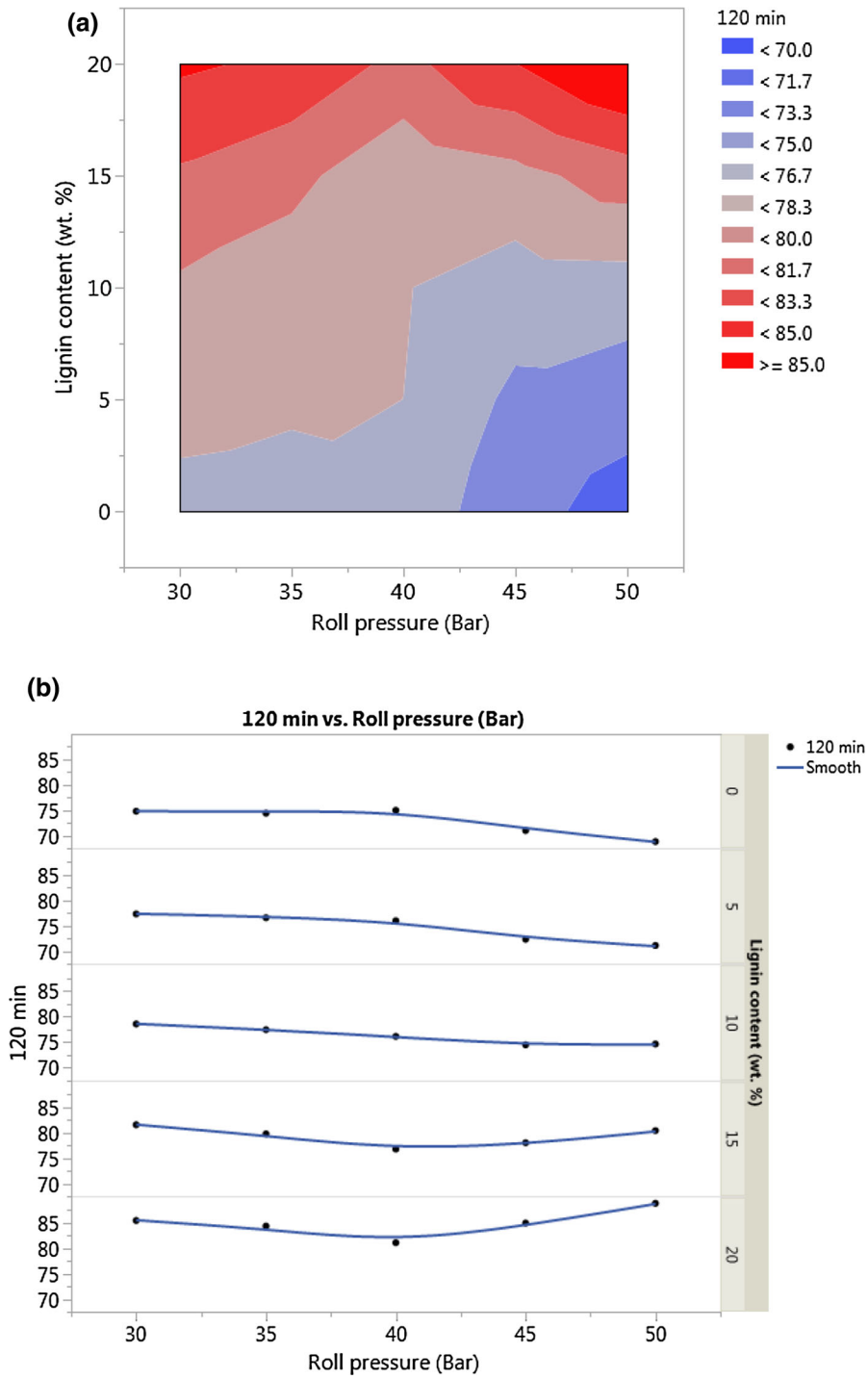

Fig. 6 Prediction profiler; **a** Contours of equilibrium drug release versus roll pressure and lignin content; **b** graph builder

Acknowledgments This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750.

Conflict of interest The authors declare that they have no conflict of interest.

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Design of Controlled Release System for Paracetamol Based on Modified Lignin

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Received: 15 April 2019; Accepted: 15 June 2019; Published: 18 June 2019

Abstract: The influence of lignin modification on drug release and pH-dependent releasing behavior of oral solid dosage forms was investigated using three different formulations. The first formulation contains microcrystalline cellulose (MCC 101) as the excipient and paracetamol as the active pharmaceutical ingredient (API). The second formulation includes Alcell lignin and MCC 101 as the excipient and paracetamol, and the third formulation consists of carboxylated Alcell lignin, MCC 101 and paracetamol. Direct compaction was carried out in order to prepare the tablets. Lignin can be readily chemically modified due to the existence of different functional groups in its structure. The focus of this investigation is on lignin carboxylation and its influence on paracetamol control release behavior at varying pH. Results suggest that carboxylated lignin tablets had the highest drug release, which is linked to their faster disintegration and lower tablet hardness.

Keywords: lignin; drug release; paracetamol; disintegration

1. Introduction

Excipients play a significant role in the final product of pharmaceutical solid dosage forms. Variations in excipient properties influence tablet processability, hardness, disintegration and bioavailability [1–3]. Nowadays, many researchers have focused their investigations on using natural biopolymers [4] in tablet manufacturing due to their biocompatibility [5,6]; they are also cheap and widely available [7–9]. Lignin is a natural biopolymer with a number of beneficial properties including biodegradability and biocompatibility [10–14]. Recently, the use of lignin is increasing as a sustainable polymer for preparing carbon fibers [15], biofuels, bioplastics and controlled release carriers [16–21]. Due to the existence of different functional groups in the lignin structure such as phenolic, hydroxyl and carboxyl groups, lignin can be chemically modified to enhance drug delivery and to control drug release [22–24]. Figueiredo et al. functionalized Kraft lignin nanoparticles by carboxylation in order to improve drug delivery of poorly water-soluble anti-cancer drugs which were pH-sensitive [18]. Lievonen et al. modified softwood Kraft lignin using a dialysis technique to improve its drug delivery performance [25]. Furthermore, it has been recognized that pH-responsive drug carriers provide superior drug delivery characteristics due to their ability to increase the stability of the active pharmaceutical ingredient (API) molecules in the stomach and release the API in the intestine [26]. Li et al. investigated the release behavior of ibuprofen using lignin-based complex micelles. The results of release tests illustrated pH-dependent and controlled release properties due to ionization of the

carboxyl groups in the lignin structure, with repulsive forces between the negatively-charged carboxyl groups of lignin and the API molecules, with higher solubility of the API at pH = 7.4 [27]. Chen et al. synthesized lignin-based pH-responsive nano-capsules to improve the controlled release of poorly water-soluble drugs by varying pH [28]. Duval et al. studied pH and light responsive behavior of controlled-release systems containing diazobenzen and modified softwood Kraft lignin [29]. Various investigations have been carried out on the effect of lignin-based polymeric nanoparticles (NPs) on the controlled release of pesticides [30,31].

Bulut et al. studied the controlled-release behavior of paracetamol using chitosan-graft-polyacrylamide microspheres via an emulsion crosslinking technique [32]. They utilized glutaraldehyde (GA) as a crosslinker to investigate its effect on the drug release rate. They mentioned the drug release rate was affected by some parameters such as the amount of GA, copolymer concentration and the composition of the drug and polymer. Their results illustrated that more controlled release of the drug occurred by increasing the GA amount and copolymer and decreasing the composition (paracetamol/polymer) ratio. Treenate et al. investigated the controlled release properties of paracetamol using a novel system composed of hydroxyethylacryl chitosan and sodium alginate in order to improve drug delivery for oral dosage forms [33]. Through improving drug water solubility, drug efficiency will be improved [34]. The current authors have evaluated the effect of lignin on the release rate of aspirin in oral dosage form, and indicated the higher release rate of drugs using lignin as an excipient in tablet formulation [9].

In this study, the effect of carboxylated lignin as an excipient on paracetamol release behavior was investigated. Lignin carboxylation was performed to enhance the carboxyl group content on the lignin surface in order to increase the interactions between the lignin and paracetamol functional groups and allow pH triggered release. To the best of our knowledge, no studies have reported the use of carboxylated lignin in paracetamol tablet manufacturing and its effect on the release. Three different formulations have been considered, one without lignin, one using pure lignin and one with carboxylated lignin. Paracetamol is utilized as a model drug in this research; it is a nonsteroidal anti-inflammatory [35]. Paracetamol is widely used as a pain relief drug as it has fast absorption within the small intestine of the human body [36,37]. Tablets were prepared by direct compaction and characterized using disintegration and dissolution tests. Modified lignin was verified using Fourier-transform infrared spectroscopy (FTIR). Drug release rates were measured using dissolution tests at pH 5.8 according to the United States Pharmacopeia (USP) [38]. In order to investigate the controlled release behavior of paracetamol, dissolution tests were carried out at acidic conditions (pH 1.2) and phosphate (pH 7.2) buffer solutions.

2. Experiments

2.1. Materials and Methods

Paracetamol (4-acetamidophenol, Phion) was used as a model API to prepare three different formulations. Microcrystalline cellulose (MCC SANAQ®101 L USP/NF/EP) and Alcell lignin (Tecnaro, Ilsfeld, Germany) were used as excipients. More details on the lignin used in this study can be found elsewhere [2,15]. Table 1 shows the composition of the three formulations considered.

Table 1. Various formulations used in this study.

Material	Formulations		
	A	**B**	**C**
Paracetamol (wt %)	20	20	20
Alcell lignin (wt %)	0	10	0
Modified Alcell lignin (wt %)	0	0	10
MCC 101 (wt %)	80	70	70

MCC = microcrystalline cellulose.

2.2. Lignin Modification

In order to allow conjugation reactions between lignin and paracetamol, lignin is functionalized with carboxylic acid groups. Synthesis of COOH–lignin involves a ring-opening reaction of succinic anhydride with 4-dimethylaminopyridine (DMAP). Lignin (2 g), succinic anhydride (2 g) and DMAP (400 mg) were added to 250 mL of tetrahydrofuran (THF) in a 500 mL round-bottom flask, followed by stirring for 48 h at room temperature [18]. The obtained carboxyl functionalized precipitate was filtered, and then, washed for 24 h using deionized water via the Soxhlet extraction system in order to remove the unreacted reagents. Finally, the modified lignin was placed in a freeze-dryer overnight. The proposed mechanism pathway [18] is presented in Figure 1.

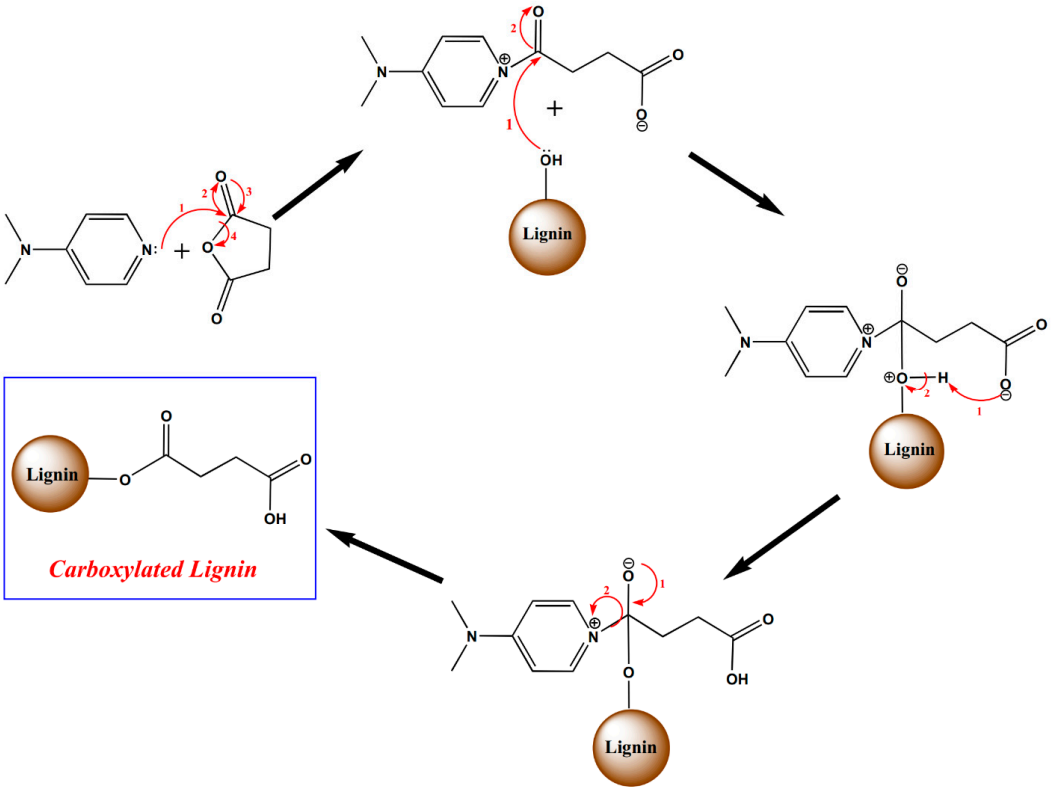

Figure 1. Mechanism of lignin carboxylation.

2.3. Tablet Preparation

In order to prepare the tablets, a single-punch tablet press (Gamlen Tableting GTD-1 D series) was utilized. Each formulation (100 mg) was compacted to make each tablet in a 6 mm die. The tablet load was set at 400 kg, with a compaction rate of 180 mm/min.

2.4. Characterisation

Fourier-transform infrared spectroscopy (FTIR) measurements was carried out utilizing a Nicolet Nexus FTIR spectrometer between 450–4000 cm^{-1} equipped with an attenuated total reflectance accessory (ATR). A total of 60 scans were performed with a spectral resolution of 2 cm^{-1}. Tablet hardness was measured using a tablet hardness tester (Pharma Test PTB311E). Pharma Test PTZ-DIST-Disintegration Test Instrument (Hainburg, Germany) was used to measure the tablet disintegration time. Deionized water (900 mL) was used to fill out the apparatus vessel and the peddle speed was kept constant at 100 rpm. The temperature of the vessel was adjusted to 37 °C. The tests were performed for the two formulations containing pure lignin and carboxylated lignin until the tablets completely disintegrated. A Pharma Test PTWS 120D 6-Station Tablet Dissolution Testing Instrument

(Hainburg, Germany) was utilized to analyze the dissolution rate of the tablets. For the measurement of drug concentration, a Cary 60 UV Spectrophotometer (Agilent Technologies, Waldbronn, Germany) was used at a wavelength of 249 nm. All tests were carried out in triplicate. The calibration graph can be found in the Supplementary Information.

2.5. Dissolution Test Procedure

Phosphate buffer with pH = 5.8 (according to USP 23) was used as the dissolution medium [38,39]; 900 mL of medium was prepared to fill each dissolution vessel. The temperature of the medium chamber and the stirrer speed were kept constant at 37 ± 0.5 °C and 50 rpm, respectively. When running the dissolution test, first, the temperature should reach 37 °C. For each run, three vessels were utilized, and one tablet was considered for each vessel. Five milliliters of sample was withdrawn at 5 min, 10 min, 20 min, 30 min, 40 min, 50 min, 60 min and 120 min from each vessel and the same amount of medium was supplant, instantly. Afterwards, the samples were filtered by applying a Captiva Econofilter (PTFE membrane, 13 mm diameter, 0.2-µm pore size). Eventually, all samples were analyzed to measure the drug concentration using a Cary 60 UV Spectrophotometer at 249 nm wavelength, which was calibrated to the optimal wavelength. The cuvette type was 1/Q/10, quartz with pathway of 1 cm. In order to minimize the statistical error, all experiments were done in triplicate. For the dissolution tests of pH-responsive analysis, due to the evaluation of the controlled release behavior of paracetamol in the carboxylated lignin formulation, two different pHs were considered: phosphate buffer solution, pH = 7.2 (intestine environment) and acidic buffer solution (0.1 N HCL), pH = 1.2 (gastric environment) [40,41].

3. Results and Discussion

3.1. FTIR Characterization of Pure Lignin and Modified Lignin

The FTIR spectra analysis was carried out to monitor the pure lignin structure and to characterize the chemical changes in the functional groups of the lignin structure during the carboxylation reactions. Figure 2 shows the spectra of pure lignin and functionalized lignin, which have similar peaks, such as C=O (carbonyl groups) at 1600 cm^{-1}, –OH (hydroxyl groups) which are attributed to the phenol and alcohol in the region of 3600–3100 cm^{-1} and an aromatic ring region at 1425–1514 cm^{-1}. Nevertheless, the hydrogen-bonded hydroxyl stretching band of carboxylic acid (2250–3600 cm^{-1}) and the stretching vibrations of C=O of the unconjugated –COOH groups at 1720 cm^{-1} exhibit a stronger absorption bond than the pure lignin (unmodified), proving that grafting lignin with carboxylic acid groups has been successfully done.

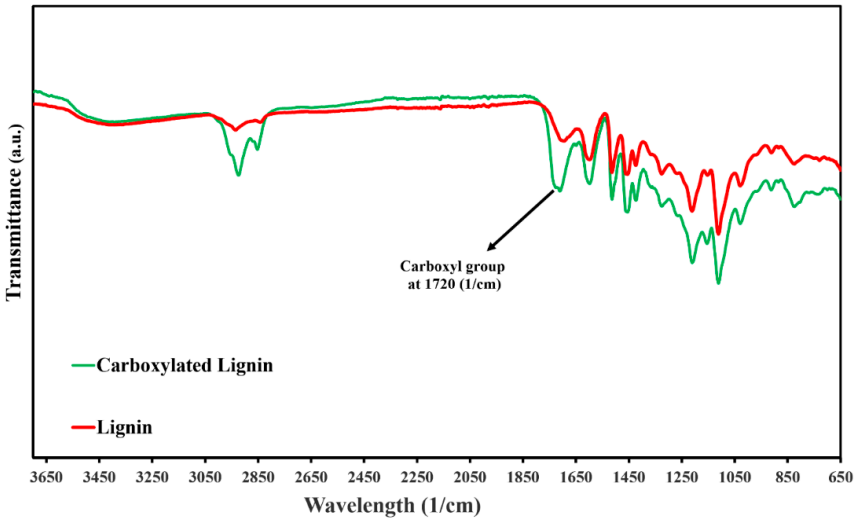

Figure 2. Fourier-transform infrared spectroscopy (FTIR) spectra of lignin (red) and carboxylated lignin (blue).

3.2. *Effect of Lignin Carboxylation on Tablet Disintegration Time*

Tablet disintegration time affects the tablet dissolution and can be used as a valuable test for solid oral dosage forms. Tablet hardness can influence tablet disintegration time, with higher hardness leading to longer disintegration times [42,43]. In order to study the effect of lignin carboxylation on the tablet disintegration time, a disintegration test was performed for the three different tablets (non-lignin, pure lignin and modified lignin). Figure 3 presents the disintegration time results in which a faster disintegration time for tablets containing modified lignin is obtained. Moreover, tablet hardness is measured using a hardness tester (Pharma Test, PTB) for three formulations, and the results show higher hardness for the formulation without lignin (Figure 4). Tablet hardness is affected by the physical properties of materials and the interaction of the drug with the excipient. The tableting method is the same for each formulation in order to mitigate its influence on tablet hardness. Generally, lower hardness equals to higher porosity; therefore, the lower hardness and higher porosity of the carboxylated lignin tablet is due presumably to the structural differences in lignin after modification.

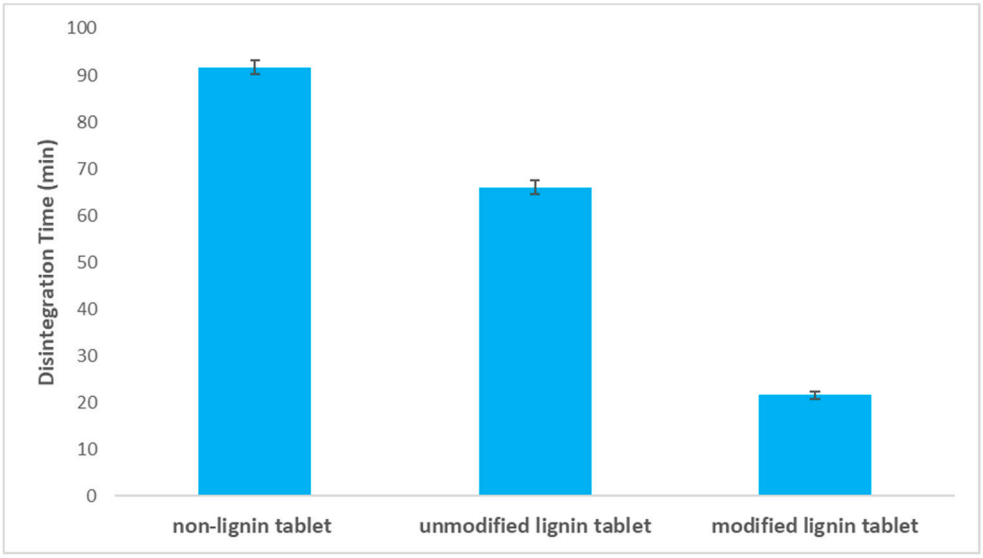

Figure 3. Disintegration time of tablets prepared containing pure lignin, modified lignin and no lignin.

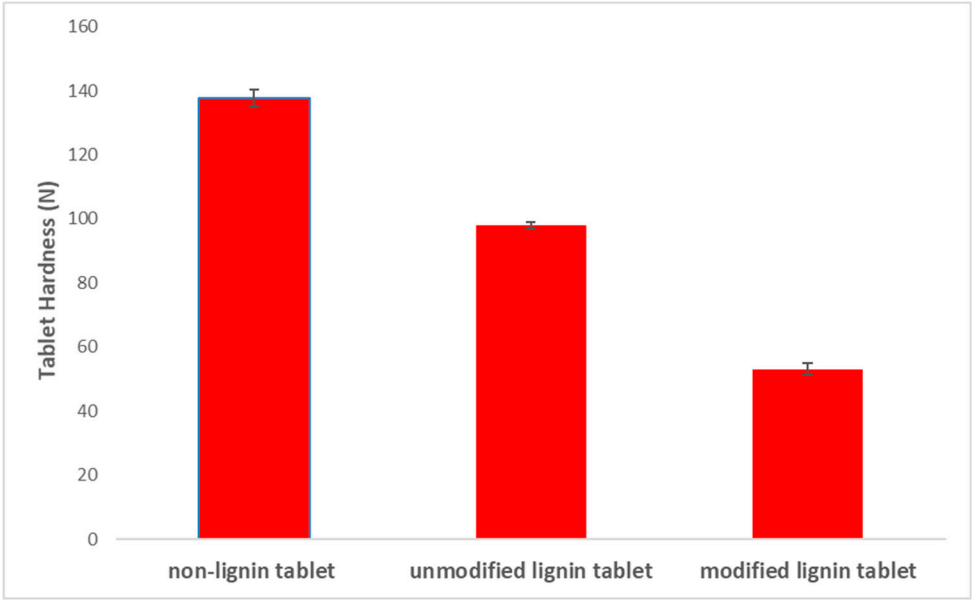

Figure 4. Hardness of tablets prepared containing pure lignin, modified lignin and no lignin.

3.3. Effect of Lignin Carboxylation on Drug Release Rate

Dissolution tests were performed to evaluate the effect of lignin and carboxylated lignin on the paracetamol tablet release rate. The three different formulations in Table 1 were considered to study paracetamol release rate in phosphate buffer solution at pH 5.8, according to the USP [38]. The release rate graphs of three different batches of paracetamol are displayed in Figure 5. Although the drug dissolution release is more dependent on the disintegration time, the formulation and material properties can influence the drug release rate. For this case, the graphs illustrate that the tablets containing functionalized lignin have the highest drug release rate and this correlates with the fastest disintegration time of these formulations and the lowest tablet hardness.

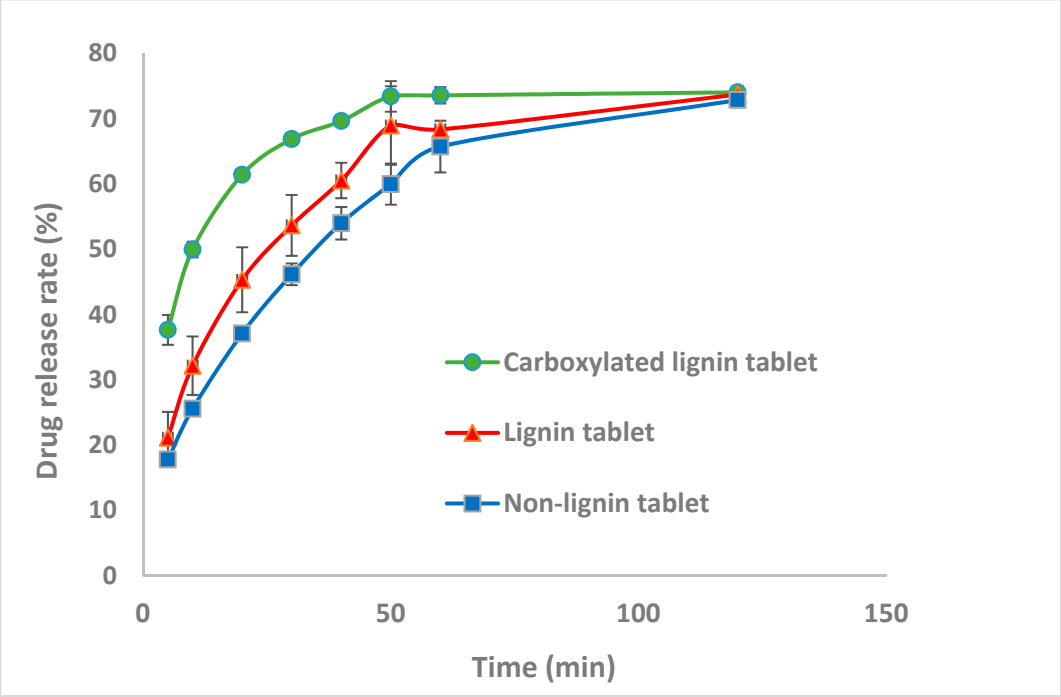

Figure 5. Drug release rate of paracetamol for the formulations at pH = 5.8.

Moreover, the prepared tablets containing pure lignin have a higher drug release rate compared to the formulation without lignin due to faster disintegration and lower tablet hardness [9]. Thus, lignin functionalization improved the release properties of directly compacted paracetamol tablets.

3.4. Controlled Release and pH-Responsive Behavior of Carboxylated Lignin

Drug release rate was studied in our previous work by adding lignin to the formulation [9]. The results revealed a higher drug release rate for the formulation containing lignin because of the amorphous structure of lignin and the interaction between lignin and the API, which resulted in an improvement in drug dissolution, which is the key factor in oral dosage development. Thus, for the present study, we have focused on drug controlled-release. The pH-responsive behavior of carboxylated lignin was investigated using dissolution tests in different media at various pH values: 0.1 M HCl solution (pH of 1.2, gastric environment) and phosphate buffer (pH 7.2, intestine environment) at 37 °C. The dissolution graphs in Figure 6 show a greater release rate of the drug in the buffer with pH = 7.2 [40]. Increasing the carboxyl groups results in an increase in drug release at pH = 7.2 compared to pH = 1.2. At pH = 1.2, the electrostatic repulsion between the lignin carboxyl groups decreases due to the protonation of carboxyl groups at lower pH values. However, at pH = 7.2, due to ionization of the carboxyl groups (pKa = 4.8) of modified lignin, the negatively-charged ions repel each other and presumably this leads to a swelling effect (similar to how hydrogels swell upon

ionization [44]) and this results in higher release rates of the API. The results of this work reveal that lignin is a promising compound for use in controlled-release systems and also for enhancing the solubility of active pharmaceutical ingredients. This is the first time that modified lignin was used for the controlled-release of paracetamol. This could be very interesting from the point of view of lignin valorization since, at the moment, the market for high value applications is very limited. The use of lignin in the pharmaceutical industry can lead to the development of new value chains for lignin promoting circular bio-economy.

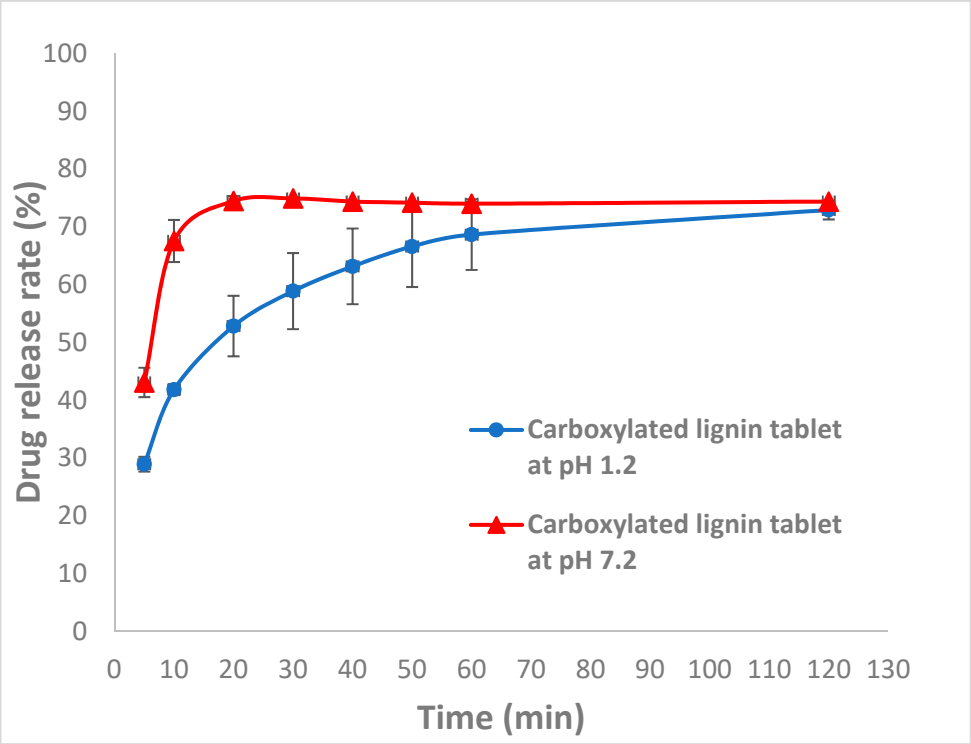

Figure 6. Drug release rate of carboxylated lignin in pH = 1.2 and pH = 7.2.

4. Conclusions

The aim of this study was to evaluate the pH-dependent release behaviors of modified lignin and the effect of lignin modification on the drug release rate. Lignin modification was conducted via carboxylation of lignin functional groups. In order to analyze the carboxyl groups in the structure of lignin and carboxylated lignin, an FTIR test was carried out and the results demonstrated a successful carboxylation. The dissolution results illustrate that there is a higher release rate of paracetamol from carboxylated lignin tablets, and this is attributed to the lower degree of interaction between lignin and the API due to the deprotonation of –COOH groups from modified lignin. Furthermore, the controlled release behavior of carboxylated lignin was evaluated at gastric pH of 1.2 and intestine pH of 7.2, and the release results showed the successful properties of controlled release. Additionally, the tablet disintegration tests showed a faster disintegration time for the carboxylated lignin tablets compared to pure lignin tablets due to the lower hardness of tablets with modified lignin. Thus, these investigations presented a successful use of carboxylated lignin natural biopolymer as an excipient in oral dosage forms for desired drug controlled-release.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4360/11/6/1059/s1.

Author Contributions: Conceptualization: M.P., M.N.C., S.S. and G.M.W.; methodology: M.P., H.H., M.N.C.; software: M.P., H.H.; validation: M.P., H.H., S.S., M.C. and M.N.C.; formal analysis: M.P. and H.H.; investigation: M.P. and H.H.; resources: M.P. and H.H.; data curation: M.P.; writing—original draft preparation, M.P. and H.H.; writing—review and editing: M.P., H.H.; validation: M.P., H.H., S.S., M.C. and M.N.C.; visualization: M.P.; supervision: M.N.C. and G.M.W.; project administration: M.N.C. and G.M.W.; funding acquisition: G.M.W.

Funding: This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750. The authors also would like to thank Rahmatullah Shaikh, Department of Chemical Sciences, Bernal Institute, Synthesis and Solid State Pharmaceutical Centre (SSPC), University of Limerick, Limerick, Ireland, for his useful comments on UV calibration.

Conflicts of Interest: The authors declare no conflict of interest.

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